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Review

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

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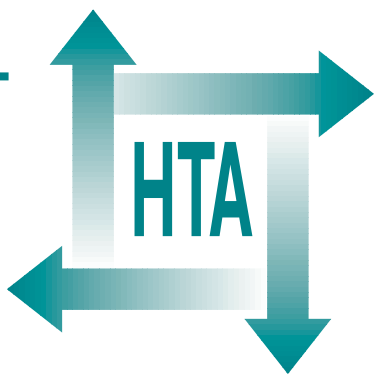
Health Technology Assessment
NHS R&D HTA Programme



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The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Acute Sector Panel and funded as project number 93/01/02.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will, in England, be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors have tried to ensure the accuracy of this report but cannot accept responsibility for any errors or omissions. They would like to thank the referees for their constructive comments on the draft document.

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Contents

List of abbreviations

ACE	angiotensin converting enzyme
ACIP	Asymptomatic Cardiac Ischemia Pilot (trial)
ACME	Angioplasty Compared with Medical Therapy (trial)
ADR	adverse drug reaction*
APSIS	Angina Prognosis Study in Stockholm
BARI	Bypass Angioplasty Revascularization Investigation
BENESTENT	Belgian and Netherlands Stent (trial)
CABG	coronary artery bypass grafting
CABRI	Coronary Angioplasty versus Bypass Revascularisation Investigation
CASS	Coronary Artery Surgery Study
CAVEAT	Coronary Angioplasty versus Excisional Atherectomy Trial
CCS	Canadian Cardiovascular Society
CCU	coronary care unit*
CEA	cost-effectiveness analysis*
CESD	Centre for Epidemiological Studies Depression scale
CHA	Canadian Heart Association*
CI	confidence interval*
CRD	Centre for Reviews and Dissemination (NHS, York)
CSAG	Clinical Standards Advisory Group
CUA	cost–utility analysis*
CVA	cardiovascular accident*
EAST	Emory Angioplasty versus Surgery Trial
ECSS	European Coronary Surgery Study
EF	ejection fraction*
EPIC	Evaluation of c7E3 for Prevention of Ischemic Complications (trial)
EPILOG	Evaluation of PTCA to Improve Long-term Outcome by c7E3 GPIIB/IIIA Receptor Blockade
ERACI	Argentine Randomised Trial of Coronary Angioplasty versus Bypass Surgery in Multi-vessel Disease
ERBAC	Excimer laser, Rotational atherectomy, Balloon Angioplasty Comparison
GABI	German Angioplasty Bypass Investigation
GI	gastrointestinal*
GP	general practitioner
GTN	glyceryl trinitrate (nitroglycerin)
HRQoL	health-related quality of life*
IHD	ischaemic heart disease
IMA	internal mammary artery
IMPACT	Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis
ISA	intrinsic sympathomimetric activity*
ISDN	isosorbide dinitrate
ISMN	isosorbide mononitrate*
ITU	intensive therapy unit*
LAD	left anterior descending
LVD	left ventricular dysfunction
LVF	left ventricular function
MAP	mean arterial pressure*
MARCATOR	Multicenter American Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis*

continued

continued

MASS	Medicine, Angioplasty or Surgery Study
MERCATOR	Multicenter European Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis
MHIQ	McMaster Health Index Questionnaire*
MI	myocardial infarction
NHLBI	National Heart, Lung and Blood Institute
NHP	Nottingham Health Profile
NS	not significant*
NYHA	New York Heart Association
PAIS	Psychological Adjustment to Illness Scale*
PGWB	Psychological General Well-Being index
POMS	Profile Of Moods States*
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality adjusted life-year
QLI-Cardiac III	Quality of Life Index – Cardiac version III*
RCT	randomised controlled trial
RITA	Randomised Intervention in the Treatment of Angina (trial)
RR	relative risk
SAQ	Seattle Angina Questionnaire
SASS	Self-Anchoring Striving Scale*
SBU	Swedish Council on Technology Assessment in Health Care
SD	standard deviation
SEM	standard error of the mean*
SF-36	Short Form (36-item) Questionnaire
SHARP	Subcutaneous Heparin and Angioplasty Restenosis Prevention (trial)*
SIP	Sickness Impact Profile
SR	sustained release*
STARC	Studio Trapidil vs. Aspirin nella Restenosi Coronarica trial
STARS	Stent Antithrombotic Regimen Study
STRESS	Stent Restenosis Study
SVG	saphenous vein grafts
TEA	endarterectomy*
TEC	transluminal extraction catheter*
TIBET	Total Ischaemic Burden European Trial
VA	Veterans' Affairs (USA)
VAS	visual analogue scale*
WAIS-R	Weschler Adult Intelligence Scale – revised

* Used only in tables and appendices

Executive summary

Objectives

To update earlier reviews of the effectiveness of treatment for chronic stable angina and to include

- assessment of medical therapy and of newer adjunctive technologies such as coronary stents
- broader assessment of patient benefits
- consideration of cost and cost-effectiveness.

Methods

Full details of the search strategy are presented in the full report.

Results

In all, 197 papers were reviewed in full – 148 relating to clinical effectiveness, 24 to health-related quality of life and 25 to cost and cost-effectiveness.

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.
- No UK cost or cost-effectiveness studies were identified.

CABG versus medical therapy

- Coronary artery bypass grafts (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 initial benefits to patients from CABG, in terms of extent of angina and activity limitation, have disappeared by 10 years.
- Available economic data reflect the results of effectiveness studies; CABG is most cost-effective where there is greatest incremental benefit – in patients with severe angina, left main disease and multi-vessel disease.

PTCA versus medical therapy

- Some evidence supports percutaneous transluminal coronary angioplasty (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.
- 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.

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 or cost-effectiveness.

Non-comparative studies of PTCA

- There is some evidence of gender differences in long-term outcomes.
- Success of PTCA is influenced by age of patient and angina class.
- PTCA can be effective in patients with left ventricular disease.
- Health-related quality of life improves after PTCA but no information is available on key subgroups.

Non-medical adjuncts to PTCA

- Results of 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; 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.
- Cost studies undertaken in the USA showed that adjunctive technologies cost more than PTCA overall. Their cost-effectiveness is doubtful.

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 PTCA 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. A cost analysis showed a 6-month difference in costs between the new drug and placebo of $293 per patient.
- The platelet-derived growth factor antagonist trapidil has been shown to be more effective than aspirin in reducing restenosis 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 restenosis.

Conclusions

Policy implications

- Healthcare purchasers and providers should consider local information, such as local epidemiological data, cost structures and available patterns of care.
- 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.
- 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.
- The provision of local evidence-based guidance to general practitioners on smoking cessation may also help improve outcomes in smokers undergoing CABG or PTCA.
- 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.
- Formal evaluation of new technologies should be considered before they become widely diffused.

Research recommendations

- Adequately-powered, long-term studies are needed of costs and effects of rational combinations of medical treatments.
- Cost and cost-effectiveness of PTCA should be compared with medical therapy.
- Relative cost-effectiveness of the new generation medical and non-medical adjuncts to PTCA and CABG, including stents, requires assessment.
- Relative cost-effectiveness of new interventions such as transmyocardial revascularisation and minimally invasive bypass grafting needs assessment.
- In stable angina, studies of patients' treatment- and health-related preferences are required.
- 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.

Chapter 1

Setting the scene for resource allocation

Background

Ischaemic heart disease (IHD) is the leading cause of death in the UK with 136,118 deaths in England in 1992 (Department of Health, 1994). The symptomatic impact of IHD is usually in the form of angina pectoris: pain in the chest, arm or jaw caused by a partial obstruction of a coronary artery by atheroma. Stable angina is said to exist when a patient experiences regular or predictable symptoms; this is distinct from unstable angina which includes new and marked anginal pain, escalating symptoms and symptoms when at rest.

A range of treatment modalities now exists for chronic stable angina. These include various medical therapies, coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA). In addition, there have been recent developments in medical and interventional adjuncts to PTCA and CABG which have the objective of increasing their clinical effectiveness. Despite the volume of studies and literature on these three broad groups of modality, there remain significant uncertainties about relative effectiveness, cost and cost-effectiveness.

The area of management of chronic stable angina has been subject to extensive review recently in the USA and Sweden. The RAND Corporation literature reviews of CABG (Leape, *et al.,* 1991) and PTCA (Hilborne, *et al.,* 1991) in the USA covered literature published from 1982 to 1990. These reviews were updated to 1993 by a report from the Swedish Council on Technology Assessment in Health Care (SBU) (Johansson, *et al.,* 1994). Together these documents provide systematic reviews of the evidence for the clinical effectiveness of these two procedures compared with medical therapy and with each other for a range of applications. However, although a general review by Gunnell and Smith (1994) has highlighted many of the issues relevant to the UK context, earlier systematic reviews neither addressed the UK situation directly nor considered the role of the newer adjunctive therapies or of medical treatment alone. Furthermore, these reviews did not assess fully the evidence of the impact of alternative technologies on costs (and hence relative cost-effectiveness) and health-related quality of life.

By systematically assessing available evidence on costs and benefits, and relating these estimates to the UK setting, the authors of this report seek to assist healthcare purchasers and provider managers in identifying the most cost-effective management strategies.

Aim of the study

The aim of this study is to build on the earlier reviews of effectiveness, while broadening the perspective and range of considerations. The additional elements included are a review of the evidence on the broader aspects of patient benefits (in the form of health-related quality of life and patients' preferences) and of cost and cost-effectiveness. The review also expands on the clinical areas covered by earlier published reviews, through an assessment of the clinical and economic impact of recent developments in each of the three broad treatment groups, including newer adjunctive technologies such as intracoronary stents.

Structure of this report

The report may be considered in three parts. The purpose of the current chapter is to provide a background to the study and to offer a context for the systematic review in terms of the epidemiology of stable angina and recent policy developments.

The systematic review itself is presented in chapters 2–11; the principal components may be summarised as follows:

- an updating of the systematic reviews of clinical effectiveness undertaken in the USA and Sweden
- a review of the evidence on health-related quality of life and patients' preferences involved in the management of stable angina
- a review of the evidence on the relative cost and cost-effectiveness of alternative treatments.

Finally, policy-relevant conclusions from the systematic review are identified in chapter 12 together with priorities for further research and development.

The epidemiology of stable angina

In order to consider the epidemiological characteristics of chronic stable angina, it is important to distinguish the burden and prognosis of IHD in general from specific symptoms in the form of stable angina. IHD is the leading cause of mortality with, as stated earlier, 136,118 deaths in England in 1992 and, although there has been a reduction in mortality since the mid-1970s, IHD still accounts for 26% of all deaths in England (Department of Health, 1994). It is responsible for 14.6% of years of life lost to age 65 in men and 5.6% of years of life lost to age 65 in women (NHS Executive, 1996).

Morbidity from angina is also considerable. The latest general practice morbidity statistics, covering the years 1991–92, provide a range of indicators of the burden of angina (McCormick, *et al.,* 1995). This survey gives an estimate of the prevalence of angina in England and Wales, defined as the number of patients who consulted their general practitioner (GP) at least once during the year for angina, of 130 and 98 per 10,000 person years at risk in men and women, respectively. In contrast to the recent decline in IHD mortality, this estimate of prevalence represents a 60–69% increase since 1981. The survey estimated that the incidence of new and first-time episodes of angina was 55 and 49 per 10,000 person years at risk in men and women, respectively. From a policy perspective, consultation rates in general practice are important as, typically, this is where patients with stable angina enter the healthcare system.

A more detailed study to estimate the incidence of angina in the general population was undertaken by Gandhi and colleagues (1995a). The study involved a random sample of 17 general practices covering a population of 191,677 in the Southampton area. All patients presenting for the first time with chest pain were referred to a special clinic for detailed assessment on the basis of clinical history and complete clinical examination. The study found an overall crude incidence of 8.3 per 10,000 (95% confidence interval (CI), 6.6–10.0) in patients aged 31–70 years. The authors applied these incidence rates to the UK population and estimated that 22,570 (95% CI, 17,840–27,030) new patients would present to their GPs with angina each year.

The utilisation of interventions

Pharmaceuticals are the mainstay of treatment for stable angina in general practice. Three main classes of drug are used to treat the condition: beta-adrenoceptor blocking drugs (beta-blockers), nitrates and calcium channel blockers. Although not used exclusively to treat stable angina, the volume of these drugs prescribed and their cost to the NHS in England in 1995 are shown in *Table 1*. This gives some indication of the burden of angina on general practice.

TABLE 1 *Prescription items dispensed for any reason and net ingredient cost of three classes of anti-anginal drug in England in 1995 (Source: Department of Health, 1996)*

Class of drug	Number of items dispensed	Net ingredient cost (£)
Nitrates	8,131,000	54,645,000
Calcium channel blockers	11,977,000	179,034,700
Beta-blockers	14,049,000	81,561,100

A survey of GP records in Nottingham found that in patients presenting to their GP with angina as defined by the prescription of nitrates, fewer than 20% were referred to hospital and, of these, half were seen by a cardiologist and just 4% underwent angiographic investigation (Cannon, *et al.,* 1988). A questionnaire sent to GPs in Hampshire found that 80% of GPs reported referring 10% or less of their patients with angina to a cardiologist, and 72% reported referring 25% or less to a hospital physician (Gandhi, *et al.,* 1995b). Thus, it is not surprising that a very small proportion of patients go on to receive PTCA or CABG; based on a median follow-up of 16 months after presentation, Gandhi and colleagues (1995a) found that 11.2% and 7.5% of patients diagnosed as having typical angina at the hospital clinic had undergone PTCA and CABG, respectively. When the denominator is the number of patients initially presenting to their GP, these rates are very much lower.

On the basis of detailed data collected for three English Regions and three Scottish Health Boards, the Clinical Standards Advisory Group (CSAG) (1993) found significant variation in rates of revascularisation procedures in 1991–92. Rates of CABG showed more than a two-fold variation, ranging from 190 per million population to 453 per million; and PTCA rates exhibited a four-fold variation, from 54 per million to 222 per million. The variation between districts was even more marked: a nine-fold variation in CABG and a 62-fold variation in PTCA was found. CSAG found that, in general, the nearer people live to a provider unit the higher the rate of use of the service.

Despite the variation in revascularisation rates, the study found that the overall rate between 1987/88 and 1991/92 had increased by between 35% (North Western region) and 575% (East Anglian region).

It has been suggested that a gender bias exists against women in terms of referral to a specialist as a result of chest pain (Tobin, *et al.,* 1987). Using data collected as part of the CSAG study, Black and colleagues (1994) identified clear differences in revascularisation rates between men and women. Rates for revascularisation were more than 3.5 times higher for men than for women in 1992/93 (3.55:1). However, Black and colleagues (1994) also found that there had been a clear reduction in the male:female ratio, from 4.2:1 in 1987/88. They suggested that the increasing rates of revascularisation in women were probably caused by clinicians perceiving revascularisation to be safer in older patients; the development of IHD in women tends to lag behind that in men by about 10 years (Lerner & Kannel, 1986).

In a survey of UK Directors of Public Health in 1994, which had a response rate of 62% covering a population of 37 million, Gunnell and Harvey (1996) confirmed the CSAG finding of considerable variation in revascularisation rates. Their survey indicated a median rate for CABG and PTCA of 355 and 156 per million, respectively; however, these rates ranged, by district, from 162 to 710 for CABG and from 18 to 648 for PTCA.

Evidence has emerged of the existence of the inverse care law in relation in revascularisation rates. Payne and Saul (1997) explored the relationship between the prevalence of angina and coronary artery revascularisation in the city of Sheffield. A strong positive correlation was found between the deprivation of an electoral ward (as measured by the Townsend score) and the prevalence of symptoms ($p < 0.001$); a similar correlation was found between premature mortality (death before 65 years of age) from IHD and deprivation. However, the study found a significant negative correlation between the ratio of revascularisation to the number experiencing symptoms and the Townsend deprivation score ($p < 0.001$); deprived wards had about half the number of revascularisations per head of more affluent wards.

In general, rates of revascularisation in the UK are markedly lower than elsewhere in the developed world. In the USA, for example, the rate of CABG is about 1200 per million and the rate of PTCA about 1300 per million (Meyer, *et al.,* 1996). In Europe, Germany, Belgium, the Netherlands and Switzerland each have revascularisation rates about 230% higher than those for the UK.

The resource implications

The true magnitude of the resource implications of treatment for stable angina is not known and the following figures should be seen as indicative rather than definitive. The Audit Commission (1995) estimated that the total NHS expenditure on coronary heart disease amounted to approximately £1000 million per annum. An earlier estimate by Langham and colleagues (1994) estimated the cost at £500 million per annum (at 1992 prices). Of course, both of these estimates include the costs associated with aspects of the disease other than treatment for stable angina.

Department of Health estimates (NHS Executive, 1996) suggest that, in 1992/93, IHD accounted for 3.1% of NHS in-patient expenditure, 1.75% of primary care expenditure and 9.0% of pharmaceutical expenditure.

Estimates of unit costs of revascularisation procedures show considerable variation, and it is difficult to establish how much of this variation reflects actual variability in costs rather than different methods of estimation. Langham and colleagues (1994) suggest that the unit cost lies in the range £5000–9000 for CABG and £3000–5000 for PTCA. But the Audit Commission has stressed the need to be aware that NHS prices (contractual or extra contractual referral) for CABG appear to vary considerably but may not be directly comparable.

McKenna and colleagues (1997) show some of the current problems in obtaining accurate estimates for the NHS cost of these procedures. Estimates of costs, based on Health Resource Group analyses, show a somewhat confusing picture (*Table 2*). These differences in cost reflect, in substantial part, the underlying variation in length of stay associated with the procedures. An additional cost driver, and an additional source of cost variation, is the use of stents which, in themselves, cost in the range £600–1000; more than one may be used in a PTCA procedure. This adds a further reason to be cautious of historical data on unit costs of PTCA procedures.

Some indication of the scale of cost associated with medical treatment is presented in *Table 1,* although this cost does not exclusively relate to the treatment of angina.

TABLE 2 *Estimates of costs, based on Health Resource Group information*

	1993/94	1994/95	1995/96
PTCA			
Overall mean length of stay, days	4.09	4.32	3.99
Elective cases:			
Median length of stay (range), days	2 (1–3)	2 (1–3)	2 (2–3)
Median cost (range), £	3.275 (1.425–3.775)	1.925 (1.250–3.800)	2.275 (1.300–3.475)
Emergency cases:			
Median length of stay (range), days	5 (2–8)	5 (2–8)	4 (2–7)
Median cost (range), £	2.050 (1.675–2.700)	2.125 (1.675–3.700)	1.725 (1.575–2.700)
CABG			
Overall mean length of stay, days	9.66	9.14	9.19
Elective cases:			
Median length of stay (range), days	8 (7–10)	8 (7–10)	8 (7–10)
Median cost (range), £	6.025 (4.900–6.350)	6.075 (5.050–6.450)	6.450 (5.900–6.825)
Emergency cases:			
Median length of stay (range), days	8 (6–11)	8 (6–10)	8 (6–10)
Median cost (range), £	5.250 (4.025–6.250)	5.350 (3.875–6.450)	6.250 (5.675–6.650)

Source: McKenna, et al., *1997 (based on data from CHKS Acute Care, 1994; 1995; 1996).*

Recent policy initiatives regarding the management of angina

The level of provision of cardiac revascularisation services has been a focus of policy debate for some years. A number of targets have been proposed although the evidence base for any of these proposed target rates is unclear. A national target of 300 CABGs per million population by 1990 was set in 1985 by the Department of Health. The Fourth Report of the Joint Cardiology Committee recommended a minimum of 400–500 per million and the British Cardiological Society's response to Health of the Nation recommended a target of 600 per million (London Implementation Group, 1993). In reviewing cardiac services in London, a specialist review group concluded that 400 CABGs per million was a minimum acceptable level and took 450 as their central assumption (London Implementation Group, 1993). In addition, the Review Team worked on the basis of a ratio of PTCAs:CABGs of 4:6.[1] The recent report of a policy review of coronary heart disease in Scotland noted that, in Scotland, activity rates now exceed 450 procedures per million population, and concluded that "purchasers would need to assess carefully the evidence on cost-effectiveness before considering a significant increase in the level of resources for CABG surgery" (Scottish Office, 1996).

[1] The proportion of PTCA/CABG procedures undertaken in the UK in 1991 was 64%; however, there are very significant international variations (Unger & Hutter, 1990).

Chapter 2

The systematic review

Introduction

This systematic review does not repeat the earlier work of RAND (Leape, *et al.*, 1991; Hilborne, *et al.*, 1991) and SBU (Johansson, *et al.*, 1994). Instead it focuses on the clinical, health-related quality of life and cost-effectiveness literature published mainly since 1993, as well as considering clinical areas not assessed adequately in the earlier reviews.

Substantial new research evidence is now available which was not published at the time of the RAND and SBU reviews. Thus, although the RAND and SBU studies are the starting point of this review, other more recent reviews within the area are also used. The review by Gunnell and Smith (1994) also provides information more relevant to the UK setting, and meta-analyses by Yusuf and colleagues (1994), comparing medical therapy and CABG, and by Pocock and colleagues (1995), comparing angioplasty and CABG, are drawn upon. There have been several recent meta-analyses examining the effectiveness of medical therapies and those of adequate quality are also reported. The results of other relevant systematic reviews or meta-analyses are included where they are of good quality. The quality criteria for assessing all of these reviews are presented in appendix 1.

Methods

Quality review of the RAND and SBU studies

The first step in this systematic review was to conduct a quality assessment of the RAND and SBU reports. The aim was to identify those areas in which the high quality systematic review of the clinical, health-related quality of life and economic evidence considered necessary for this study had or had not been carried out. The RAND and SBU reports were 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). The results of the quality assessment are summarised in appendix 1.

On the basis of the results of this quality assessment, the following general approach has been followed in the current study.

- Given the limitations of the search strategy used in these earlier reviews of clinical effectiveness, a full search (see below) has been undertaken over their joint period of analysis (1982–93) with the aim of identifying any key studies that these reviews missed. The implications of any missing key articles for the conclusions of these reviews has been considered.
- A full search strategy on clinical effectiveness has been employed for the period following the RAND and SBU studies (1993–December 1996), thus updating these earlier reviews.
- To broaden the perspective taken by the RAND and SBU studies, cost-effectiveness and health-related quality of life have been built into the search strategy and followed throughout the full review period (1982–96).
- Because of the intensity and importance of new clinical papers appearing as this review was being prepared, the formal search for papers on clinical effectiveness was updated to December 1997.
- Where potentially important papers have been identified which have been published since the main literature searches were completed, details are included in footnotes.

Search strategy

The search strategy employed was developed using standard systematic review techniques to obtain clinical and economic evidence. Guidelines published by the NHS Centre for Reviews and Dissemination (CRD), York University, were used to ensure that the most robust review techniques were incorporated into the study (NHS CRD, 1996).

The search strategy had five principal components. These were:

- sources of evidence (that is, the databases searched)
- inclusion and exclusion criteria for studies
- methods for data extraction
- data synthesis
- assessment of quality of evidence.

Sources of evidence

The range of databases interrogated covered relevant medical, pharmaceutical, economic, sociological, organisational and methodological evidence. Full details of the search terms used to interrogate MEDLINE, and then adapted to search the other databases listed in *Table 3,* are given in appendix 2.

In addition to the systematic review of primary studies, good quality systematic reviews and meta-analyses have been included if they had evidence of a literature search strategy, explicit inclusion criteria, validity assessment of primary studies and appropriate pooling or summary. The systematic reviews themselves were identified from NHS CRD DARE (Database of Abstracts of Research Evidence) database, in which the results of reviews from 1994 onwards are reported. Systematic reviews before this period were identified from MEDLINE using a recommended search strategy (NHS CRD, 1996). An Expert Panel was convened to provide advice on the review; it was comprised of cardiologists, cardiac surgeons, an academic GP, commissioners and specialists in public health. The Expert Panel met once and provided detailed feedback on earlier drafts of the review and drew attention to papers not identified in the formal search.

Inclusion and exclusion criteria

In this review, data from randomised controlled trials (RCTs) are emphasised, when appropriate, since trials provide the best evidence of efficacy because of greater control over confounding factors and a high degree of **internal validity**. However, the narrow inclusion criteria used in RCTs can lead to a reduction in **external validity** (generalisability) – an essential characteristic for the assessment of effectiveness and cost-effectiveness from a purchasing perspective. Relative effectiveness in routine practice may be better assessed using more naturalistic observational studies. As this type of evidence can often better inform questions of cost-effectiveness, this review has extended assessment of evidence beyond that offered by RCTs to include large observational studies.

The following inclusion criteria have been used in this review.

For non-drug clinical studies, one of the following:

- RCT
- UK-based observational study (> 1000 patients or comparative)
- North American, Australasian or European observational study (> 1000 patients).

For drug clinical studies, both of the following:

- between-class comparison[1]
- RCT with a follow-up at least 6 months.

For cost and cost-effectiveness analyses, one of the following:

- comparative economic evaluation looking at costs and outcomes
- comparative cost analysis looking at full range of costs
- non-comparative cost analysis looking at full range of costs – UK only.

TABLE 3 *Databases searched in the systematic review*

Clinical effectiveness	MEDLINE Health Planning and Administration (National Library of Medicine, USA) NHS CRD DARE database BIDS (Bath Information and Dissemination Service Cochrane Library Dissertation Abstracts Online (UMI, USA) EMBASE PsycINFO (American Psychological Association) Social SciSearch (ISI, USA)
HRQoL	MEDLINE
Cost and cost-effectiveness	MEDLINE Health Planning and Administration Office of Health Economics database (HEED) NHS CRD economic evaluation database

[1] Placebo-controlled trials were only included as primary studies if at least two classes of drugs were compared in the study. Some placebo-controlled trials are included in some of the meta-analyses reviewed here.

For analysis of health-related quality of life and patient preferences, one of the following:

- analysis of health-related quality of life using a formal quantitative instrument
- analyses of patients' preferences.

In all cases only English language studies could be reviewed, given limited resources.

Inclusion of studies and data extraction

Initial trawl Focusing on those titles and abstracts identified by the database search strategy, a first initial trawl through the literature was undertaken to exclude those articles that plainly did not fulfil the inclusion criteria. A second trawl of articles not excluded was undertaken on titles and abstracts by two researchers, with disagreements being settled by a third.

Main review Articles not excluded after both trawls were acquired as hard copy and the extent to which they satisfied the inclusion criteria was assessed by one researcher. The remaining articles were then checked against those included in the earlier RAND and SBU reviews (1982–93), and only those articles not covered by these earlier studies entered the main review. Data were extracted by one reviewer.

Quality assessment of included studies

Quality assessment of all the clinical, health-related quality of life and economic studies included in the review was undertaken.

The assessment of included **RCTs** was based on a published checklist (NHS CRD, 1996). The assessment covered the following six dimensions.

- Randomisation – was the assignment to the treatment groups really random?
- Completeness of follow-up – was relatively complete follow-up achieved? To avoid the possibility of excluding information in areas where there have been few trials published, 80% was taken as a cut-off point (this does not imply, however, that this degree of attrition is generally acceptable in trials).
- Withdrawals – were the outcomes of people who withdrew described and included in the analysis?
- Blinded assessment of outcomes – were those assessing the outcomes of patients blind to the treatment allocation?
- Comparable groups – were the control and treatment groups comparable at entry?
- Were the groups treated identically, other than for the named interventions?

Quality assessment was carried out by one reviewer.

The quality of **observational studies** was assessed using a checklist for observational studies (NHS CRD, 1996). Among other factors, the validity of the study is likely to depend on the length and completeness of follow-up and the extent to which cohorts are comparable (i.e. on confounding variables), the use of explicit inclusion criteria and the use of objective criteria to assess outcomes. The results of the quality assessments are presented in the appendices to this document, with the main findings described briefly in the following chapters.

The following criteria were used for the assessment of observational studies.

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

Studies focusing on **health-related quality of life** have been subject to quality assessment at two levels. First, the design of the study itself (i.e. the data collection process) has been subjected to the same quality review as the studies of clinical effectiveness (either RCTs or observational studies as detailed above). Second, an attempt has been made to assess the quality of the instruments used in studies. Criteria are less well-developed for this aspect of studies and it was not feasible to subject each instrument used to a formal quality assessment. Therefore, the quality assessment of health-related quality-of-life instruments indicates whether the instrument(s) used were reviewed by Bowling in either 1991 or 1995. These papers together represent a extensive review of a large number of condition-specific and generic health-related quality-of-life questionnaires and provide an independent critique.

In the case of **economic** studies, the quality assessment of cost and cost-effectiveness analyses adopted was based on the 35-point checklist developed by Drummond and Jefferson (1996) to assist referees of economic studies submitted to the *BMJ*.

Results

Details of the numbers of papers identified from the initial database searches are presented in appendix 3, including the papers rejected (with reasons) and those remaining in the detailed review. In the clinical review, a total of 5414 articles were identified, of which 4687 were excluded on the basis of titles and abstracts leaving 727 articles to be obtained as hard copy. Of these, 580 were excluded, leaving 147 to be reviewed in full.

A total of 227 articles were identified for the health-related quality-of-life part of the study, of which 187 were excluded on the basis of titles and abstracts, leaving 40 full articles to be obtained. Of these, 19 were excluded, leaving 21 to be reviewed in full.

A total of 211 articles relevant to cost and cost-effectiveness were identified, of which 151 were excluded on the basis of titles and abstracts, leaving 60 articles to be obtained in full. Of these, 36 were excluded, leaving 24 to be reviewed.

A summary of the results are presented under the following headings in chapters 3–10:

- medical treatments (chapter 3)
- medical treatments compared with PTCA and CABG (chapter 4)
- PTCA compared with CABG (chapter 5)
- non-comparative observational studies of CABG only (chapter 6)
- use of medical adjuncts to CABG (chapter 7)
- non-comparative observational studies of PTCA only (chapter 8)
- non-medical adjuncts to PTCA (chapter 9)
- medical adjuncts to PTCA (chapter 10).

An overall summary of the main findings is presented in chapter 11.

Chapter 3
Medical treatments

Introduction

Before being considered for revascularisation, most patients presenting with angina will be treated medically. The RAND and SBU reviews of alternative treatments for angina did not consider the evidence relating to drug therapy. However, there have been several good quality systematic reviews published more recently, in which the effectiveness of medical therapies has been examined; these are discussed below. The current review also considers available evidence on health-related quality of life and cost-effectiveness.

Clinical effectiveness

Previous systematic reviews and meta-analyses

The effectiveness of calcium channel antagonists has been examined in at least three systematic reviews. Opie (1988) reviewed 41 trials in which the effectiveness of verapamil, nifedipine and diltiazem was examined, both compared with each other and with propranolol; he concluded that verapamil (120–360 mg daily) was effective in the treatment of stable angina, and that high doses of verapamil (360–480 mg daily) were more effective than propranolol. Nifedipine (60 mg daily) was more effective than placebo in increasing exercise time and, in longer-term studies (up to 28 days), in reducing angina attack rate and nitroglycerin (glyceryl trinitrate, GTN) usage.

Nifedipine treatment was compared with beta-blockade in five studies and, in four studies, nifedipine appeared to be less effective than beta-blockers, although it was unclear what outcomes were being assessed. Nifidepine was also associated with a higher incidence of side-effects. Diltiazem (240–360 mg daily) appeared to be as effective as propranolol at the same dosage over a short period (2–4 weeks). There was little to choose between beta-blockers and calcium channel antagonists in terms of effectiveness, although the latter group appeared to have fewer side-effects and contra-indications. The trials, however, were limited by relatively short follow-up periods, with most reporting outcomes at less than 6 weeks.

The issue of safety has also been highlighted with respect to nifedipine by Furberg and colleagues (1995) in a meta-analysis of 16 RCTs. Overall, the use of nifedipine was associated with a significant adverse effect on total mortality (risk ratio, 1.16; 95% CI: 1.01–1.33), although there was a strong dose-response relationship; for daily doses of 30–50, 60 and 80 mg, the risk ratios (95% CI) for total mortality were 1.06 (0.89–1.27), 1.18 (0.93–1.50) and 2.83 (1.35–5.93), respectively. High doses of nifedipine were significantly associated with increased mortality ($p = 0.01$). However, this review has been strongly criticised from a clinical perspective on methodological grounds (Lichtlen, 1996; Messerli, 1996), hence the results should be interpreted with caution.

Singh (1992) examined the safety profile of the calcium channel antagonist bepridil as an anti-anginal agent by pooling the results from 11 American trials and found adverse effects on the gastrointestinal and central nervous systems, although most reactions did not result in discontinuation of therapy. However, there are few data on the inclusion criteria used in these trials or on the inclusion criteria used in the review itself.

Trials of antiplatelet agents have also been subjected to several methodologically robust meta-analyses. Sacks and colleagues (1990) analysed 11 trials (published between 1960 and 1970) of the efficacy of dipyridamole in the prevention and treatment of chronic stable angina, and found a combined effect favouring dipyridamole over placebo. However, there is great heterogeneity among the included trials, with duration of treatment ranging from 2 weeks to 7 months and daily doses ranging from 37.5 mg to 225 mg. It is not clear exactly what constituted improvement in the primary studies.

The effectiveness of antiplatelet therapy was also examined in two reviews. Rigorous review methods were employed, including the inclusion of individual patient data (as opposed to published summary data). In the first of these, unconfounded RCTs of prolonged antiplatelet therapy versus control in the prevention of death, myocardial infarction (MI) and stroke were analysed (Anti-

platelet Trialists' Collaboration, 1994a). Trials of all agents acting on the vascular system by inhibiting platelet aggregation were included. The analysis of patients with stable angina showed a non-significant trend in favour of a reduction in MI, stroke or vascular death associated with treatment, although the total number of patients included was relatively small (five trials with < 300 patients in the treatment group). However, it was evident that antiplatelet therapy could offer protection against MI, stroke and death in a wide range of patients at high risk of occlusive vascular disease. Significant benefit was evident not only among patients with unstable angina, suspected acute MI or a past history of MI, stroke or transient ischaemic attack, but also in other categories of patients at high risk, such as those with stable angina.

A review of primary evidence

The effectiveness of medical therapies in the treatment of chronic stable angina was not examined in the RAND and SBU reviews (although comparisons of medical therapy with angioplasty and CABG were eligible for inclusion). The present review, however, includes inter-class, RCT-based comparisons of anti-anginal medical therapy with follow-up periods of 6 months or more. Studies reporting comparisons between calcium channel antagonists, beta-blocking agents and nitrates or other drugs were, therefore, eligible for inclusion. Intra-class comparisons between specific agents (for example, between different types or doses of beta-blockers, calcium channel antagonists or nitrates) and one class versus placebo were excluded. However, comparisons between ordinary beta-blockers and beta-blockers with some other level of mode of activity, such as intrinsic sympathomimetic activity, were included. Combinations of drugs were also included.

Ten RCTs were identified for inclusion. The actual drugs examined in these comparisons were:

- beta-blockers – propranolol, metoprolol, epanolol, atenolol, carvedilol and nadolol
- nitrate – isosorbide dinitrate (ISDN)
- calcium channel antagonists – bepridil, diltiazem, nifedipine and amlodipine
- potassium channel activator – nicorandil.

Two studies examined combinations of drugs: beta-blocker plus calcium channel antagonist (Kawanishi, *et al.,* 1992) and beta-blocker plus nitrate (Nahrendorf, *et al.,* 1992). Two studies included beta-blockers with some other action: a vasodilating beta-blocker (Nahrendorf, *et al.,* 1992), and a beta-blocker with intrinsic sympathomimetic activity (Boberg, *et al.,* 1992). Most of these studies were small, with sample sizes of fewer than 200, although the largest study had a sample size of 608. The lengths of follow-up varied from the minimum required to meet the inclusion criteria (6 months) to a maximum of 3 years in the Total Ischaemic Burden European Trial (TIBET) studies (Dargie, *et al.,* 1996; Fox, *et al.,* 1996).

A range of outcomes was assessed – most commonly exercise tolerance, angina incidence, MI rate and vessel narrowing. These outcomes and all adverse events reported are summarised in appendix 4.

Beta-blockers versus calcium channel antagonists

Direct comparisons between these drug classes were reported in four studies. No evidence of differences in effectiveness between drugs was found (see appendix 4). Destors and colleagues (1989) found no difference between propranolol, 60–240 mg daily, and bepridil, 100–400 mg daily, at 6 months in terms of either increased exercise duration or workload, although both were significantly better than placebo. Vliegen and colleagues (1991) similarly found metoprolol, 100 mg twice daily, and diltiazem to be equally effective at 32 weeks in increasing exercise tolerance, while in another study nadolol, 40–160 mg daily, and amlodipine, 2.5–10 mg daily, were found to be equally effective in terms of increase in exercise time, time to angina onset, ST segment depression and angina incidence at 28-week follow-up (Singh, *et al.,* 1993).

In the TIBET study (Dargie, *et al.,* 1996), atenolol was compared with nifedipine at a mean of 2 years follow-up; no group differences were found in primary endpoints (cardiac death, non-fatal MI, need for revascularisation, unstable angina) or secondary endpoints (exercise duration, onset to angina).

Adverse effects were reported for the comparisons between propranolol and bepridil, and between nadolol and amlodipine. In the case of propranolol and bepridil, there were no differences in numbers of fatal or severe non-fatal events, although less severe cardiovascular events were more commonly reported with bepridil use (Destors, *et al.,* 1989). There were no differences between groups in terms of non-cardiac events (including psychiatric side-effects). Overall, side-effects were more commonly associated with nadolol than with amlodipine (Singh, *et al.,* 1993). These included bradycardia (40% versus 3%) and dizziness (25% versus 13%).

No information on adverse effects was reported for the comparison between metoprolol and diltiazem. The TIBET study showed a higher withdrawal rate with nifedipine treatment compared with atenolol because of side-effects (Dargie, *et al.,* 1996).

The Angina Prognosis Study in Stockholm (APSIS), a multicentre trial in which the beta-blocker, metoprolol, was compared with the calcium channel blocker, verapamil, in a group of 809 patients aged under 70 years with a history of stable angina (Rehnqvist, *et al.,* 1996). The study was designed to examine not only cardiovascular endpoints but also psychological outcomes reflecting health-related quality of life. At follow-up (which ranged from 6 to 75 months), the two treatments did not differ in proportion of deaths or non-fatal cardiovascular events, and Cox regression analysis showed that at no point in time was there a difference between treatments. Most of the patients in both groups were in angina New York Heart Association (NYHA) angina classes I and II, with a similar duration of angina (about 2 years). About one-third of patients overall were women and 22% were smokers, with the verapamil group having a higher proportion of women and non-smokers. However, adjustment for gender and smoking did not alter the results significantly.

Combinations of beta-blockers and calcium channel blockers

In two RCTs, beta-blockers or calcium channel blockers were compared with combinations of both drugs. Kawanishi and colleagues (1992) reported comparisons between propranolol and nifedipine and a combination of both. Doses of individual drugs were the maximum tolerable by the individual. The combination showed no greater effectiveness in angina reduction at 6 months, compared with either drug alone. Similarly, exercise tolerance showed no benefit with combination therapy. However, combination therapy was associated with fewer painful episodes ($p < 0.05$), although there were no group differences in the total number of episodes or in the number of silent episodes. Side-effects were not reported.

The multicentre RCT by Dargie and colleagues (1996) (TIBET study) compared the beta-blocker atenolol with the calcium channel blocker nifedipine and with a combination of both drugs in over 600 patients. Follow-up ranged from 1 year to 3 years, with a mean of 2 years. No difference between single and combination drug therapy was found in terms of either the primary or secondary endpoints described above.

Side-effects did not differ between atenolol and combination therapy, although nifedipine alone was associated with a higher incidence of side-effects.

Beta-blockers with other action

Two studies were found in which the long-term effectiveness of beta-blockers with additional action was examined. In the first of these, epanolol (a beta-blocker with intrinsic sympathomimetic activity) was compared with atenolol at 6 months follow-up (Boberg, *et al.,* 1992). No significant differences in angina attack rates, exercise tolerance or measures of health-related quality of life were observed. However, adverse effects such as dizziness and fatigue were significantly less common with epanolol. In the second study, a vasodilating beta-blocker carvedilol, 25 mg twice daily, was compared with a propranolol/ISDN combination, 80 mg/20 mg twice daily (Nahrendorf, *et al.,* 1992). Although there were greater short-term benefits associated with the combination therapy, as assessed by exercise tests, only carvedilol showed any maintenance of improvement in function at 6 months. Although dropouts and adverse effects differed slightly between treatments, the numbers of patients involved were very small and the differences non-significant.

Beta-blockers versus nitrates

Only in one study was the long-term effectiveness of these drugs compared. Loaldi and colleagues (1991) randomised 80 patients matched for duration of angina and extent of disease to either propranolol, 80 mg four times daily, or ISDN, 40 mg four times daily. All patients had greater than 50% stenosis of a major coronary artery with a narrowing of less than 50% of one or more other major branches. Progression of the disease was defined as a 20% or more increase in obstruction or change from less than 100% obstruction to 100% obstruction in any vessel. At 2-year follow-up, disease had progressed in both groups, with progression more common in those treated with propranolol (70% versus 48%, $p < 0.05$). The authors suggested that increases in serum lipid values may have played a role in producing this difference between the groups.

Calcium channel blocker versus potassium channel activator

In a study by Guermonprez and colleagues (1993), diltiazem, 180 mg daily in three doses, was compared with nicorandil, 20 mg daily in two divided doses for two weeks followed by 40 mg daily for the rest of the study. At 6 months there was no difference between groups in terms of exercise

tolerance or angina frequency. The overall rates of adverse event were similar for both groups, although the profile of events reported was different: diltiazem was associated with gastrointestinal disorders while nicorandil was associated with headache.

Quality of included studies

The quality of clinical effectiveness studies is shown in appendix 13. The overall quality of the included drugs trials was high. In all cases, authors presented information explicitly to demonstrate the comparability of treatment and control groups and, as far as could be determined from the information presented, the groups received identical treatment. All studies presented detailed information on patients withdrawing from trials. However, the method of randomisation was often unclear and in only one study was a required sample size calculated. Given this, and the small size of the majority of the studies, the reported lack of differences in effectiveness between treatments may have been due to lack of statistical power. Lack of systematic reporting of adverse outcomes was also a feature of many of the trials, making it difficult to generalise about differences in safety.

Health-related quality of life

One study has been identified in which the impact of different classes of anti-anginal drugs on health-related quality of life are compared (see appendix 4 for details). The study is a large RCT (n = 427) by Fletcher and colleagues (1988), in which GTN, 5 mg transdermal patches, and placebo are compared in patients with chronic stable angina of at least 3 months duration which is inadequately controlled by beta-blockers. Two health-related quality-of-life measurement instruments were used: the Sickness Impact Profile (SIP) and the Health Index. At 8-week follow-up, there were no clinical differences between the groups – the reduction in angina attack rate was the same for both groups. The SIP showed no health-related quality-of-life benefit from transdermal GTN; on the contrary, the adverse effects of the drug resulted in a greater overall improvement in SIP scores for patients on placebo, due principally to the effect of the active drug on the social interaction dimension of the instrument.

The RCT is of good quality (withdrawals assessed and included, relatively complete follow-up, and blinded assessment of outcomes) with one important exception; despite randomisation, the groups differed significantly at the start of the study, with a higher proportion of MIs and greater reported dysfunction in the placebo group. The SIP was reviewed by Bowling (1995) but not the Health Index.

Details are also given in appendix 4 of the results of a study examining patient preferences within two randomised crossover trials, one comparing a beta-blocker with intrinsic sympathomimetic activity (epanolol) with a standard beta-blocker (metoprolol), and the other comparing a beta-blocker with intrinsic sympathomimetic activity with a calcium channel blocker (nifedipine). In the first trial, 39% of patients preferred epanolol compared with 33% who preferred metoprolol and 28% who had no preference (n = 552 evaluable patients). In the second trial, a statistically significantly higher proportion of patients preferred epanolol (39%) to nifedipine (25%) ($p < 0.001$), with 36% of patients having no preference (n = 490 evaluable patients).

Cost and cost-effectiveness

Only one study has been located in which the relative cost and cost-effectiveness of the medical treatments for angina are considered (see appendix 4). In an American study, Larrat (1994) used a model to compare the annual cost of three forms of nitrate therapy: ISDN (the standard nitrate therapy), GTN transdermal patches and isosorbide mononitrate. The model focused on the overall cost of therapy, which added the cost of treatment failure, in terms of additional drugs and possible revascularisation, to the costs of the nitrates themselves. The results indicated that overall, because of better tolerance and less need of dosing titration, isosorbide mononitrate is 16% less costly than the GTN patch and 28% less costly than ISDN. Larratt reported the average cost per treatment success (defined as total control of angina symptoms), which was lowest with isosorbide mononitrate.

The quality of the study is open to doubt in a number of areas (see appendix 13). Perhaps most importantly, the overall costs were not disaggregated fully and the sensitivity analysis was limited.

Conclusions

It would appear that few differences in these classes of drug have been found in direct comparisons. However, many of the studies were likely to lack the power to detect a difference where one existed. It is also evident (see appendix 13) that there

have been few head-to-head comparisons between classes of medical therapies in long-term treatment. Beta-blockers have been compared with calcium channel antagonists in four trials of reasonable quality. Studies in which beta-blockers with vasodilating action and intrinsic sympathomimetic activity were examined showed no evidence that they were more effective than ordinary beta-blockers. The long-term effects of beta-blockers with other modes of action have similarly been under-researched. The main differences reported concerned adverse effects, with side-effects much more common with nadolol treatment than amlodipine in one study. However, in half of these studies little or no information on adverse effects was reported, making it difficult to estimate relative safety of these treatments.

The study in which health-related quality of life was considered showed the negative impact of adverse events on health-related quality of life. Another study of patients' preferences alongside a crossover trial showed that a higher proportion of patients preferred a beta-blocker to a calcium channel blocker (but 36% had no preference). No UK cost or cost-effectiveness studies were identified. The one American study found was of limited quality and focused solely on nitrate therapy.

Chapter 4

Medical treatments compared with PTCA and CABG

The first-line treatment for patients presenting with angina is usually medical therapy. The development of surgical and percutaneous forms of revascularisation has provided increased options for patients with stable angina. The evidence that has recently accumulated on the comparison of medical therapy with PTCA and CABG is described in this chapter.

Comparison of medical therapy and CABG

Clinical effectiveness

The results of three RCTs undertaken in the early 1980s comparing CABG with medical therapy were detailed in the RAND and SBU reviews. The overall conclusions of these studies, the Veterans Affairs (VA) Cooperative Study, the European Coronary Surgery Study (ECSS) and the Coronary Artery Surgery Study (CASS), were as follows.

- CABG generated greater improvement in angina between 1- and 5-year follow-up but this difference had disappeared by 10-year follow-up.
- No marked difference in MI rate was observed overall at 5-year follow-up, except in patients with three-vessel disease undergoing CABG who suffered significantly fewer MIs than those on medical therapy.
- CABG was shown to produce better survival than medical therapy in patients who had left main disease with greater than 50% stenosis, three-vessel disease with reduced left ventricular function (LVF), two-vessel disease with proximal left anterior descending (LAD) artery involvement or two- or three-vessel disease with a strongly positive exercise stress test.
- The SBU review cast doubt on the generalisability of these results given the relatively youth of the patients and the lack of women in the trials. However, SBU reports a study in which 780 patients randomised to the CASS study were compared with 1319 other patients who were suitable for the trial and the results are consistent with those in the trial.

However, these early randomised trials of CABG versus medical therapy may be outdated because of improvements in medical therapy and surgical techniques. A meta-analysis by Yusuf and colleagues (1994) has been carried out since the SBU reviews. This compared the effects of a strategy of routine CABG with one of initial medical therapy in patients with stable coronary heart disease on mortality at 5, 7, and 10 years. Individual patient data were pooled from trials in which patients were randomly assigned to CABG surgery or medical treatment, and patients were grouped according to risk status (severity of angina, history of hypertension or MI, and ST depression at rest). The overall mortality was lower in the CABG group than in patients assigned to medical therapy. The overall odds ratio for total mortality was 0.61 (95% CI, 0.48–0.77) at 5 years, 0.68 (95% CI, 0.56–0.83) at 7 years and 0.83 (95% CI, 0.70–0.98) at 10 years.

The data were also analysed in patient subgroups and, for left main artery disease, the odds ratio for total 5-year mortality was 0.32 (95% CI, 0.15–0.70); for patients with three-vessel disease it was 0.58 (95% CI, 0.42–0.80). For patients with one- or two-vessel disease the odds ratio was 0.77 (95% CI, 0.51–1.15). Mortality in the CABG group was significantly reduced in patients with proximal LAD stenosis. In patients without disease of the proximal LAD, mortality was significantly reduced only in patients with three-vessel or left main artery disease. The treatment effects of CABG were similar in patients with normal or abnormal LVF, and were also similar in patients with different severity of angina classes. However, as the mortality rate was higher in patients with low ejection fractions, the absolute benefit of surgery was greater in those with poor LVF.

Analyses were also carried out to compare benefits in subgroups at high and low risk. Treatment benefit was found to be greater in patients at high risk; the odds ratio for total mortality at 5 years was 0.50 (95% CI, 0.35–0.72) for patients at high risk, 0.63 (95% CI, 0.39–1.01) for patients at medium risk, and 1.18 (95% CI, 0.51–2.71) for patients at low risk. Overall, a strategy of initial CABG was associated with lower mortality than medical

therapy with delayed surgery if necessary, especially in patients at high and medium risk. In patients at low risk, the limited data showed a non-significant trend towards greater mortality with CABG. This finding of greater proportional benefit for patients at high risk is confirmed by an American observational study of 5824 patients, with a follow-up of 15–20 years (Muhlbaier, *et al.,* 1992). This study also showed a greater probability of event-free survival in CABG patients than in medical patients, after adjustment for baseline prognostic factors.

Several further papers reporting the results of RCTs which compared medical therapy and CABG have been identified, and these are summarised in appendix 5. They include further follow-up of the VA (VA Coronary Artery Bypass Surgery Cooperative Study Group, 1992) and CASS (Alderman, *et al.,* 1990) trials. The VA trial showed no significant difference in survival at 18 years or in the incidence of angina at 15 years; however, non-fatal MI was higher in CABG patients. The CASS study also showed similar survival rates at 10 years but no difference in MI rates.

Two of these additional studies showed a clear mortality benefit to CABG patients at 5 years (Palac, *et al.,* 1981; Frick, *et al.,* 1983) and at 10 years (Palac, *et al.,* 1981; Hwang, *et al.,* 1990). The findings of these studies were not replicated by Bhayana and colleagues (1980). There are some methodological shortcomings with two of these trials; the studies by Bhayana and colleagues and Palac and colleagues had less than 80% follow-up; also, the latter study did not clearly describe its withdrawals. The study by Frick and colleagues was, however, of high quality.

Focusing on patients in the VA trial with left main disease, Takaro and colleagues (1985) found that surgery has a clear survival benefit at 3.5 years, especially in patients with severe narrowing of the arteries, impaired LVF and multiple risk factors. However, the overall quality assessment of the study was low. One small RCT (n = 26) compared medical treatment with CABG in 26 patients with insulin-dependent diabetes (Manske, *et al.,* 1992). The trial was too small to generate any clear conclusions but, methodologically, is of good quality, with relatively complete follow-up of participants, withdrawals assessed and included in the analysis, and description of blinded assessment of outcomes. The VA trials are of similar good quality. Most other trials also included full details of withdrawals and appear to analyse patients in the groups to which they were originally randomised. The Takaro trial, however, only partially accounted for crossovers from medical to surgical treatment (by censorship of some data).

An additional observational study fulfilling the inclusion criteria and comparing CABG and medical therapy has been identified in the literature; it, too, is summarised in appendix 4 (Gersh, *et al.,* 1985). The study is based on the CASS registry and focuses on patients over 65 years of age. It indicates a clear survival advantage for CABG at 6 years ($p < 0.0001$). However, this study is likely to exhibit bias because of inadequate control over patient case-mix and its results should be considered with caution.

A large prospective study comparing survival among patients receiving medical therapy, angioplasty or CABG is described in chapter 5 (Jones, *et al.,* 1996b). In this study either CABG or angioplasty was found to provide better long-term survival than medical therapy at all levels of disease severity. RCTs in which medical treatment is compared with both CABG and angioplasty are discussed later in this chapter.

Health-related quality of life

No studies comparing CABG and drug therapy and looking at health-related quality of life with a formal instrument have been identified in the literature. However, one large RCT was identified in which the effects of medical therapies were compared with revascularisation in terms of patient-based outcomes – the CASS study (Rogers, *et al.,* 1990). Given the dearth of formal health-related quality-of-life data in this area, the study by Rogers and colleagues has been included to give some indication of the relative impact of the two interventions on non-clinical outcomes (see appendix 4).

In this study, 780 patients with at least 70% stenosis of one or more operable coronary arteries were randomised to either medical treatment by their referring physicians or CABG. At entry, equal proportions of patients were allocated to beta-blockers and nitrates; other drug therapies were also used including GTN and calcium channel blockers. Although proxies for health-related quality of life, such as angina relief, activity limitation and reduction in use of anti-anginal medications, favoured the surgical group at 1- and 5-year follow-up, the differences had attenuated by 10 years. The authors suggested, however, that this effect actually reflects the major impact of late CABG in patients initially receiving medical care. Censored analyses excluding these 'late-surgery' patients supported this interpretation.

In terms of the quality of this study, three drawbacks are apparent.

- The study lacks blinded assessment of outcomes.
- The groups were not treated identically following randomisation; that is, it was not possible to manipulate the other medical therapies used by the patients for up to 10 years follow-up. However, an analysis of drug use at baseline and 1, 5 and 10 years shows that only GTN use differed between medical and surgical groups at years 1 and 5 only. Use of other pharmaceuticals, including calcium channel blockers, tranquillisers, antiplatelet and antihypertensive drugs, anticoagulant and anti-arrhythmic drugs, did not differ significantly between groups.
- The study did not used validated instruments measuring health-related quality of life; instead a range of symptom and function measures was used.

Cost and cost-effectiveness

The RAND review gives details of a study undertaken to compare the relative cost-effectiveness of CABG and medical therapy (Weinstein & Stason, 1982) (see also appendix 5). Measuring benefits in terms of quality adjusted life-years (QALYs), the study showed that the incremental cost per additional QALY with CABG over medical treatment was lower in subgroups with severe angina and in two- or three-vessel disease or left main disease. The study used effectiveness data from the major RCTs but the fact that it was undertaken some 15 years ago using American cost data must cast doubt on its validity to a UK population.

A further economic study comparing the cost-effectiveness of CABG and medical therapy is summarised in appendix 5. Williams (1985) evaluated both treatment strategies in a UK context in terms of expected costs and QALYs. The study confirmed the results of the earlier American study in showing that the incremental cost of CABG over medical therapy, per additional QALY, was lower in severe angina with left main disease and 3-vessel disease. By today's standards of economic evaluation, the study exhibits a number of weaknesses. For example, health state values and some of the clinical parameters were based on clinical opinion.

In a modelling study from the USA, Wong and colleagues (1990) compared conservative therapy (medical therapy initially followed by revascularisation if symptoms persisted), angioplasty and CABG. This study is described in detail later in chapter 5 and appendix 7. The authors concluded that revascularisation is only cost-effective if the patient has severe symptoms, others markers of substantial ischaemia or severe multi-vessel disease.

Charles and colleagues (1982) undertook a comparative cost-analysis of medical therapy and CABG alongside the CASS trial but using patient data only from one trial centre (see appendix 5). Not surprisingly, the study found that hospital charges during the first year were significantly higher in surgical patients than medical ones. The facts that it used charges rather than costs, that it was based in the USA and had a small sample size, and that it was based on data that was nearly 20 years old, again limit the usefulness of the results of this study for UK policy makers.

Conclusions

It appears clear from previous meta-analyses and systematic reviews and from the majority of recently published RCTs that there are long-term mortality benefits to CABG over medical therapy, particularly in patients with greater extent of disease. This difference is evident for up to 5 years and possibly also for longer periods of follow-up (up to 10 years).

No studies formally assessing health-related quality of life with a standardised instrument have been identified in the literature. One study was found which showed that initial benefits to patients from CABG, in terms of extent of angina and activity limitation, had disappeared by 10 years.

The economic data relating to the comparison of CABG and medical therapy are limited in the extent to which they reflect contemporary clinical and economic factors in the UK health service. The three full cost-effectiveness analyses were, when published, considered to be of high quality. Their results reflect the results of effectiveness studies; the greater incremental benefit is generated by CABG in patients with severe angina, left main disease and multi-vessel disease, and this is reflected in lower incremental cost per additional QALY ratios for CABG in relation to these subgroups.

The comparison of medical therapy and angioplasty

Clinical effectiveness

At the point at which the RAND and SBU reviews were completed, few studies had been undertaken to assess the relative effectiveness and cost-effectiveness of medical therapy and

angioplasty. The publication in the USA in 1992 of the VA trial, in which medical treatment (n = 107) was compared with angioplasty (n = 105) in patients with stable angina and single-vessel disease, provided the only data on this key comparison (Parisi, *et al.,* 1992) (the Angioplasty Compared with Medical Therapy (ACME) trial). The trial showed a 4.8% MI rate in angioplasty patients compared with 2.8% in medically treated patients. On the basis of 6 months follow-up, the trial indicated that angioplasty offered earlier and more complete relief of angina (64% angina-free versus 46%, $p < 0.01$), albeit at the cost of a greater risk of re-intervention (16% of PTCA patients required a second angioplasty).

Since that trial, three further studies have been published, details of which appear in appendix 6. Pepine and colleagues (1994) randomised patients to angina-guided medical therapy, ischaemia-guided medical therapy and revascularisation (either coronary angioplasty or CABG) (details are also reported by Rogers and colleagues, 1995a). This study found some indication that revascularisation is associated with lower mortality and MI at 1-year follow-up and that this was maintained at 2 years (Davies, *et al.,* 1997), but the authors concluded that a larger trial was needed to confirm these results. In terms of quality, follow-up seems to have been complete with no withdrawals, although there is too little methodological information given to assess other aspects of the study. (The 1995 Asymptomatic Cardiac Ischemia Pilot (ACIP) publications by Bourassa and colleagues (1995a; b) are not discussed here as the report overlaps to a large extent with the earlier study by Pepine and colleagues in 1994.)

Hueb and colleagues (1995) compared medical therapy, angioplasty and CABG in 214 patients with stable angina and single-vessel disease in the LAD artery. Although all three strategies had similar rates of mortality and MI at an average follow-up period of 3 years, angioplasty and CABG resulted in greater improvement in angina. In terms of angina and subsequent revascularisation, CABG showed better results. The study is methodologically sound (complete follow-up, withdrawals adequately dealt with, randomisation resulting in comparable treatment groups, though without blinded outcome assessment).

The Randomised Intervention in the Treatment of Angina (RITA)-II trial (RITA Trial Participants, 1997) has shown that the advantages of angioplasty over medical therapy in relief of symptoms are greatest in patients with more severe angina at baseline. However, the high rate of restenosis in angioplasty patients meant that, after approximately 3 years, there was little difference between the treatments in this respect. There appeared to be little benefit for patients with few symptoms. This is confirmed by the long-term results from the ACME trial, in which patients with two-vessel disease were followed-up for up to 6 years; long-term symptom-related and quality-of-life outcomes of angioplasty or medical therapy were found to be comparable (Folland, *et al.,* 1997).

One large prospective study comparing survival in patients receiving medical therapy, coronary angioplasty or CABG is described in chapter 5 (Jones, *et al.,* 1996b). Either CABG or angioplasty were found to provide better long-term survival than medical therapy at all levels of disease severity, while angioplasty offered greater benefit than CABG in patients with single-vessel disease, except in those with at least 95% proximal LAD stenosis.

Health-related quality of life

The RAND and SBU reviews contained no details of studies of health-related quality-of-life studies which compared coronary angioplasty and drugs. The current review has identified three such studies (see appendix 6). One, undertaken by Strauss and colleagues (1995), was carried out alongside the ACME RCT detailed above (Parisi, *et al.,* 1992). Using the McMaster Health Index and the Psychological General Well-Being index (PGWB), the study concluded that patients randomised to angioplasty experienced a significantly greater improvement in health-related quality of life ($p = 0.02$) at 6 months. This was reflected in improvements in both psychological and physical functioning, which favoured angioplasty patients at 6-month follow-up. This improvement in health-related quality of life was found to be related to improvements in exercise tolerance and angiographically-detected improvements in lesion severity. The RCT itself is of good quality: details of randomisation are given separately, follow-up is relatively complete, withdrawals are accounted for, and blinded assessment of outcomes reported. Both health-related quality-of-life instruments were reviewed by Bowling (1995).

The two other relevant studies are by Spertus (1994; 1995), who developed a brief functional status measure for use in patients with coronary artery disease, the Seattle Angina Questionnaire (SAQ), and has reported on its use in two prospective series of patients undergoing angioplasty. It is unclear whether patients in the earlier study also appear in the later study. However, the 1995

study is mainly concerned with validating the scale rather than monitoring the health-related quality of life of patients, so only the 1994 study is discussed here. Briefly, in 45, mainly male, patients with a mean age of 60 years functional status improved over 3 months. Short Form (SF-36) data also indicated that physical and mental health had improved. Again, however, the data presented focuses mainly on the validity of the scale rather than on changes in health-related quality of life in this small group; for example, there is little information presented on the baseline clinical status of these patients. It is difficult, therefore, to draw clear conclusions from the results.

In terms of the quality of the study, one point in particular should be noted – the patients seem to be a highly selected group, chosen on the grounds that they were expected to show great improvement in health-related quality of life. Their representativeness is, therefore, unclear. However, in other respects the study is of acceptable quality, with adequate follow-up and objective assessment of outcomes. The SAQ is not reviewed by Bowling (1991; 1995) but is in common use.

Cost and cost-effectiveness

One study has been identified which directly assesses the relative cost-effectiveness of angioplasty and medical therapy (see appendix 6). Using clinical data from the ACME RCT (see above) and cost data relating to the Australian health service, Kinlay (1996) looked at relative costs and effects (patients free of angina) over a 3-year period in patients with single-vessel disease. The study found a net additional social cost per patient of angioplasty of A$479; the net cost of angioplasty to the hospital of A$1109 was partly offset by savings to the Federal Government and to the patient. The overall incremental cost of angioplasty per additional patient free of angina was A$3875. The study concluded that angioplasty may be more cost-effective than medical therapy. The quality of the study may have been compromised by the conflation of cost and charge data and the risk of double counting.

In addition to this study, the American modelling study referred to above compared conservative therapy (medical therapy initially followed by revascularisation if symptoms persisted), angioplasty and CABG (Wong, *et al.*, 1990). This study is described in detail in the next chapter and in appendix 7. The authors concluded that revascularisation is only cost-effective if the patient has severe symptoms, others markers of substantial ischaemia or severe multi-vessel disease.

Conclusions

The clinical studies comparing angioplasty and medical therapy show some evidence supporting angioplasty in terms of relief of angina but the evidence in terms of MI rates is conflicting. This clinical benefit is also apparently reflected in improved health-related quality of life, although information on long-term effects of revascularisation is lacking. In one Australian cost-effectiveness analysis, angioplasty was considered cost-effective on the basis of an incremental cost per extra patient free of angina of A$3875.

Chapter 5

PTCA compared with CABG

Introduction

For a proportion of patients with stable angina, either angioplasty or CABG is clinically feasible. For these patients, the relative effectiveness and cost-effectiveness of the two interventions is uncertain. Until recently no RCT had been undertaken which compared angioplasty and CABG in this group of patients but over the last few years several RCTs have been published, and these continue to provide valuable follow-up data. The results of the systematic review relating to the comparison of coronary angioplasty and CABG are reported in this chapter.

Clinical effectiveness

In assessing the relative effectiveness of angioplasty and CABG, the RAND and SBU reviews relied largely on observational data. The SBU review was able to include some details of three of the new trials. Details of two of these – the Argentine Randomised Trial of Coronary Angioplasty versus Bypass Surgery in Multiple Vessel Disease (ERACI) and the German Angioplasty Bypass Investigation (GABI) trials – were described in abstract form only. However, SBU was able to report two-year follow-up in the UK study, the RITA trial (RITA trial participants, 1993). RITA showed no significant difference in the combined end-point of deaths and MI ($p = 0.47$). However, angina rates were higher in angioplasty patients at 6 months ($p < 0.001$) and at 2 years ($p = 0.007$). Over a mean follow-up of 2.5 years, 18.8% and 18.2% of angioplasty patients required a CABG and a repeat angioplasty, respectively; the rates for patients randomised to CABG were 0.8% and 3.2%, respectively. However, only 3% of patients undergoing an angiogram in participating hospitals during the recruitment period of the trial were randomised to RITA.

The focus of the RAND reviews was on the observational studies undertaken to compare the two modalities, with the results of three observational studies described. These clearly indicated a higher subsequent intervention rate in angioplasty patients but were more equivocal as regards event-free survival rates. In reviewing more recent observational studies, SBU reported the results of a study in the USA of 96,666 Medicare patients. The study showed survival benefits from angioplasty in patients at low risk as a result of lower short-term mortality. In summarising the evidence, SBU emphasised the heterogeneity of patients with stable angina and how this will often influence the choice between angioplasty and CABG. For example, patients with a single stenosis of the LAD artery would be ideal candidates for angioplasty, whereas patients with triple-vessel occlusions would typically be more appropriate for CABG. Uncertainty exists in some subgroups, which SBU argues are quite small.

Since 1993, the pattern of published clinical comparisons of angioplasty and CABG has altered. The search undertaken for this review has identified seven published RCTs comparing the two interventions in addition to the RITA trial. The characteristics and clinical results of these studies are summarised in appendix 7; the appendix also summarises the RITA trial as the study is also used as a vehicle for clinical and economic assessment. All of the larger trials (ERACI, GABI, Coronary Angioplasty versus Bypass Revascularisation Investigation (CABRI), Emory Angioplasty versus Surgery Trial (EAST)) only include patients with multi-vessel disease; the smaller Medicine, Angioplasty or Surgery Study (MASS) and Lausanne studies include randomised patients with single-vessel disease only. The RITA study (from which the results of the 5-year follow-up are due to be published in late 1998) considers both single- and multi-vessel disease.

Pocock and colleagues (1995) synthesised the data from the trials detailed in appendix 7 in a meta-analysis, having contacted each principal investigator for data. Sim and colleagues (1995) have also undertaken a meta-analysis of the data from the ERACI, RITA, CABRI, GABI and EAST trials, although without retrieval of original patient data; the results are essentially the same as those of Pocock and colleagues. The detailed systematic review by Gunnell and Smith (1994), summarised in appendix 1, has some overlap with the review by Pocock and colleagues. Other systematic reviews exist in this area (e.g. Filart & Ryan, 1993) but have been superseded by publication of more recent reviews and trials.

The review by Pocock and colleagues (1995) highlighted the following results from the trials.

- No evidence of a statistically significant difference in mortality at any point in time was identified in any of the trials in isolation or in the pooled analysis, with a relative risk (RR) of PTCA:CABG of 1.08 (95% CI, 0.79–1.50).
- Similarly, there was no evidence of a significant difference in the combined outcome of cardiac death plus non-fatal MI, either within individual trials or overall. Although fewer patients undergoing angioplasty experienced cardiac death or an infarction during hospitalisation (4.2% versus 5.4%; $p = 0.09$), the total of these events during the first year was similar (RR of PTCA:CABG, 1.03; 95% CI, 0.84–1.27).
- Patients randomised to CABG were found to be less likely to require further therapeutic interventions in all of the eight published RCTs. During the initial hospitalisation, 4.4% and 1.6% of patients randomised to angioplasty required an emergency or elective CABG, respectively. Within the first year 17.8% of angioplasty patients required a CABG. During the first year 33.7% of angioplasty patients required at least one repeat angioplasty and/or CABG compared with only 3.3% of CABG patients. However, there was considerable heterogeneity between the trials, possibly due, in part, to the fact that regular angiograms were part of the follow-up protocol in some trials and this may have increased the rate of re-intervention. After the first year, the difference between the randomised groups in additional procedures was less pronounced.
- All trials showed a higher prevalence of angina (grade 2 or more on the Canadian Cardiovascular Society Classification (CCSC)) after 1 year in patients randomised to angioplasty (RR of PTCA:CABG, 1.56; 95% CI, 1.30–1.88). However, three of the trials in the meta-analysis were able to provide 3-year data, at which point the difference in angina rates had reduced markedly (RR, 1.23; 95% CI, 0.99–1.54).
- There was little evidence of difference in treatment effect between subgroups of patient with single-vessel disease and patients with multivessel disease, though the meta-analysis had limited power to detect such a difference in treatment effect.
- Comparing the results in single- versus multivessel disease, the meta-analysis showed that, in the first year, the risk of cardiac death or MI was lower in patients randomised to CABG than in those allocated to angioplasty in patients with single-vessel disease. No such distinction was found in patients with multi-vessel disease. However, given the relatively small number of patients involved in this subgroup analysis, the result needs to be interpreted with caution. Furthermore, the results of a large American observational study conflicts with this finding (see below; Jones, *et al.,* 1996b). No major differences were found to exist in rates of additional procedure between the two disease subgroups. Although angina rates at 1 year and 3 years were lower in patients with single-vessel disease in both randomised groups ($p < 0.01$), RRs for angina in angioplasty patients compared with CABG patients are not significantly different between the two disease groups.

Since Pocock and colleagues' (1995) meta-analysis, the results from the Bypass Angioplasty Revascularization Investigation (BARI) have been published (BARI investigators, 1996). BARI is the largest RCT of PTCA and CABG undertaken as yet, as well as having the longest follow-up period. In general, the results of the BARI trial are consistent with those of the earlier studies, as angina prevalence was higher at 5 years and revascularisation more likely with angioplasty.

The 3-year follow-up data from the ERACI trial has also been published and the results generally concur with those of the above meta-analysis; freedom from angina was greater in the group receiving CABG and there was less need for further interventions, although there were no differences in overall mortality or MI rates (Rodriguez, *et al.,* 1996).

However, one large comparative observational study in the USA compared survival outcomes of patients undergoing CABG, angioplasty and medical therapy (Jones, *et al.,* 1996b). In this study, analysis was undertaken of clinical and angiographic data collected since 1971 on 9263 patients with one-, two- or three-vessel disease that had been confirmed by cardiac catheterisation. Patient follow-up data was 97% complete and the follow-up period was up to 10 years. After statistical adjustment for baseline differences, either angioplasty or CABG were found to provide better long-term outcomes than medical treatment at all levels of disease severity, while patients with one-vessel disease (apart from those with at least 95% proximal LAD stenosis) showed a greater benefit with angioplasty than CABG. Patients with three-vessel disease, and those with two-vessel disease and at least 95% proximal LAD stenosis benefited more from CABG than angioplasty. Survival benefit was similar for either revascularisation procedure in all other patients with two-vessel disease and in

patients with at least 95% proximal LAD stenosis only. The absolute survival benefit was found to be greatest in patients with severe three-vessel disease treated with CABG compared with similar patients undergoing angioplasty.

The value of this study is that it is likely to include patients who are more representative of those in routine practice than the selective trials[1] while being more informative for decision makers than the non-comparative observational studies.

Health-related quality of life

The RAND reviews did not consider patient-based measures of outcome in any level of detail. The SBU review emphasised that most studies looking at patient-based outcomes used freedom from angina and return to work as indicators of health-related quality of life. No studies comparing coronary angioplasty and CABG were reviewed.

A total of three studies were identified in which angioplasty and CABG are compared; details of these studies are presented in appendix 7. The BARI trial has supported a quality-of-life assessment and 5-year follow-up data are available (Hlatky, *et al.,* 1997). Improvement in functional status, as measured by the Duke Activity Status Index was significantly greater in CABG patients after 1-, 2- and 3-year follow-up periods but not after 4 years. There were no significant differences throughout follow-up between the two groups in improvement in emotional health, as measured by the RAND Mental Health Inventory. The other studies shown are all relatively small observational studies.[2]

On the basis of this limited group of studies, the following points can be made.

- In only one of the studies (Papadantonaki, *et al.,* 1994) were statistically significant differences found in health-related quality of life between patients undergoing angioplasty and those having CABG. The study found that angioplasty patients experienced a greater improvement in mood and physical functioning between baseline and 3-weeks post-hospital discharge. However, it is likely that this short period of follow-up will have resulted in the instruments picking up the continued effects of the longer convalescence experienced after CABG. The short follow-up, the small sample size and the non-experimental design suggest caution in the interpretation of the results of this study.
- In terms of design, the RITA trial offers the greatest internal validity of the health-related quality-of-life assessments. A generic health-related quality-of-life instrument was employed, the Nottingham Health Profile (NHP) but no significant differences were found between the PTCA and CABG groups 2 years after initial surgery, although patients who underwent surgery had slightly better scores on all dimensions of the instrument.
- Although patients' perceptions of the impact of revascularisation on their health-related quality of life is an important aspect of the effectiveness of angioplasty and CABG, studies undertaken to date have failed to provide clear results. This has been caused by poor study design, small numbers, short follow-up periods and poor instrument selection.
- The health-related quality-of-life components of the RITA-1 and BARI trials, however, show a firm correlation between angina and patients' health-related quality of life (Pocock, *et al.,* 1996; Hltatky, *et al.,* 1995). Therefore, the collection of data on angina in clinical studies may facilitate some in-direct assessment of health-related quality of life. Both are good quality studies, in terms of providing detailed inclusion criteria, sufficient length of follow-up, objective assessment of outcomes and inclusion of patients at similar stage of disease. The instruments used in these studies were reviewed in Bowling (1995) (see appendix 13).

Cost and cost-effectiveness

The RAND review considered some early evidence on the relative cost of angioplasty and CABG. The review summarises the results of a study by Reeder and colleagues (1984) which looked at the charges associated with the two procedures in single-vessel disease and found that the initial charges associated with angioplasty were $5500 (including surgical

[1] An important limitation of the trials comparing PTCA and CABG is the small proportion of patients who were screened for the trials and included in these studies. Overall, it has been estimated that the trials are focusing on about 10% of patients presenting for treatment with actual or suspected coronary artery disease, and these studies achieved a 50% recruitment rate in this group of patients (Rickards & Davies, 1995).

[2] The EAST trial has reported data which it describes as relating to health-related quality-of-life measurements (Weintraub *et al.,* 1995c). However, this analysis has been excluded from the current review as it does not use a formal instrument.

standby) compared to $12,000 for CABG (at 1980 prices); however, the cumulative charge differential reduced by the end of 1 year: $11,400 compared with $13,400. Berreklouw and colleagues (1989) looked at actual costs and found that cost differences reduced markedly beyond 2 years.

The results of other cost and cost-effectiveness studies published since 1985 are summarised in appendix 7, and include three cost-analyses undertaken alongside RCTs. Both the RCT-based and observational studies show a marked difference between angioplasty and CABG in the initial cost of the two treatment strategies. This point is emphasised in *Figure 1,* in which the various estimates that have been published of the cost of angioplasty, as a proportion of the cost of CABG, are shown at various points of follow-up, using data presented in a recent review article update (Goodman, 1996). Those studies which report estimates of relative cost at points of follow-up as well as the initial relative cost, demonstrate how the higher rate of re-intervention in patients undergoing angioplasty increases the cost of this form of management relative to CABG.

The considerable variation in estimates of relative cost of angioplasty and CABG at initial intervention is shown in *Figure 1* (i.e. at 0 years). This spread partly reflects the different cost items included in the various analyses. Furthermore, patterns of resource use and costs differ markedly by country. Out of all the studies reviewed in appendix 7, only one relates to UK practice – the cost analysis undertaken alongside the RITA trial (Sculpher, *et al.,* 1994). With an initial mean cost of angioplasty of 52% that of the cost of CABG, a proportion that increased to 81% at 2 years, the cost estimates from this study lie in the mid-range of those published.

Only one study has been identified in the literature in which the relative cost-effectiveness of angioplasty and CABG has been assessed (Wong, *et al.,* 1990).[3] In this study, also summarised in appendix 7, a decision-analytical model and the synthesis

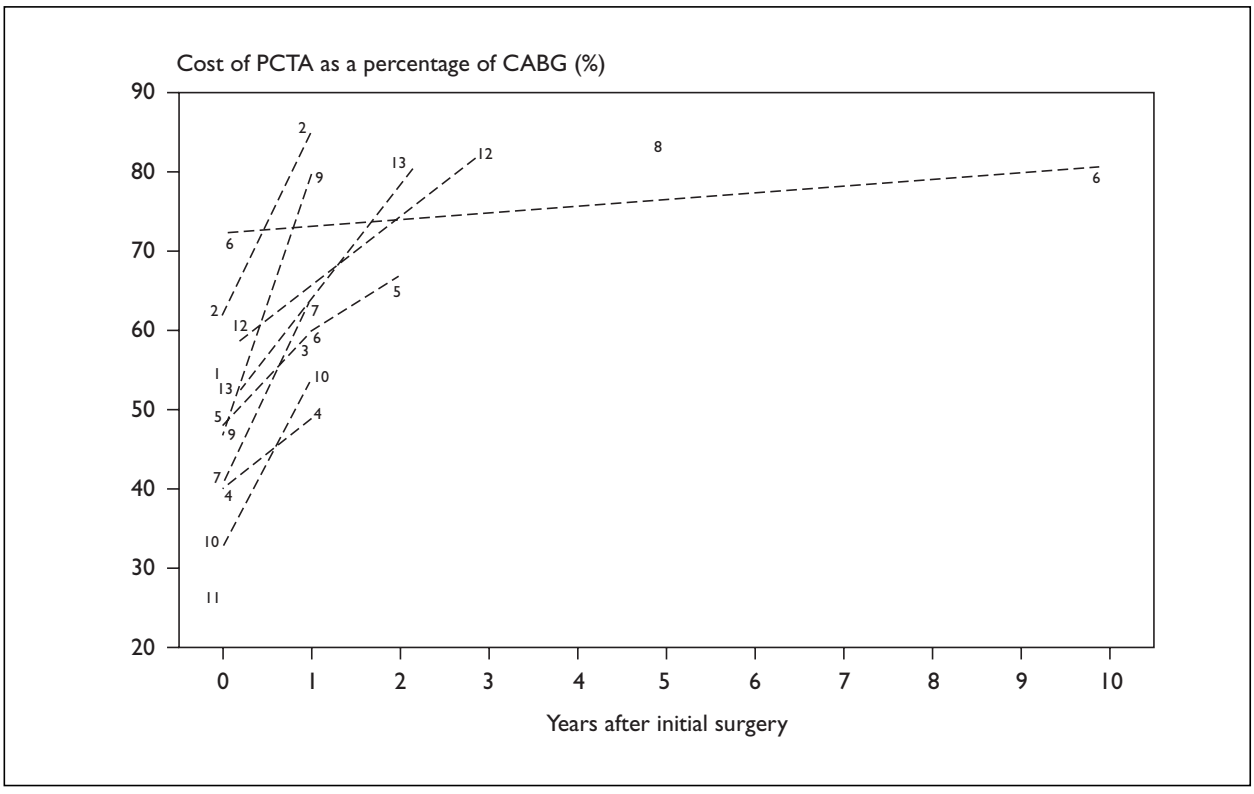

FIGURE 1 *Cost of PTCA as a percentage of the cost of CABG over time based on primary studies (1 = Jang,* et al., *1984; 2 = Reeder,* et al., *1984; 3 = Kelly,* et al., *1985; 4 = Black,* et al., *1988; 5 = Berreklouw,* et al., *1989; 6 = NHTAP, 1989; 7 = van den Brand,* et al., *1990; 8 = Wittels,* et al., *1990; 9 = Hlatky,* et al., *1990; 10 = Rodriguez,* et al., *1993; 11 = Cohen,* et al., *1993; 12 = Weintraub, et al., 1995c; 13 = Sculpher,* et al., *1994) (Source: Goodman, 1996)*

[3] A cost-effectiveness analysis has been published since the formal literature search based on 5-year follow-up data from the BARI trial (Hlatky, *et al.,* 1997). By 5 years, patients randomised to CABG had a higher mean cost ($58,889 versus $56,225) but a slightly higher survival rate (0.10 life-year). This resulted in an incremental cost per life-year gained of $26,117.

TABLE 4 *Summary of results of analysis by Wong and colleagues (1990) (shows most cost-effective form of management for a given subgroup)*

	Normal ventricular function		Depressed ventricular function	
	Mild angina	**Severe angina**	**Mild angina**	**Severe angina**
1-vessel disease	Conservative therapy	PTCA	Conservative therapy	PTCA
2-vessel disease	PTCA[a]	PTCA	PTCA[b]	PTCA
3-vessel disease	PTCA[a] CABG[b]	PTCA[c]	PTCA[a]	PTCA[c]
Type C lesion or incomplete PTCA revascularisation	Conservative therapy	CABG	Conservative therapy	CABG

[a] *High incremental cost-effectiveness ratio (i.e. extra cost per additional QALY).*
[b] *Very high incremental cost-effectiveness ratio.*
[c] *If completely revascularisable.*

of data from a range of sources was used. The analysis compared three management strategies: CABG, angioplasty and conservative therapy (no revascularisation unless symptoms continue). The results showed that the most cost-effective form of management depended on the patient's baseline clinical characteristics, and these findings are summarised in *Table 4*. As shown in the table, the authors concluded that angioplasty is likely to be more cost-effective than CABG as long as complete revascularisation is possible, which may not be feasible in patients with three-vessel disease. Given that the analysis was undertaken in the late 1980s using (mainly observational) clinical data from the mid- to late-1980s, the exact results of the analysis should be treated with some caution. However, given the dearth of analyses of the relative cost-effectiveness of angioplasty and CABG, the broad conclusions of the study may be of some assistance to decision makers.

Conclusions

No differences have emerged between angioplasty 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 after surgery, and appears to be more effective in relief of angina. After statistical adjustment for baseline differences, the results of a large observational study indicated that patients with single-vessel disease (apart from those with at least 95% proximal LAD stenosis) showed a greater benefit from PTCA than CABG. Patients with three-vessel disease, and those with two-vessel disease and at least 95% proximal LAD stenosis, benefited more from CABG than angioplasty.

Survival benefit was similar for either revascularisation procedure in all other patients with two-vessel disease and in patients with at least 95% proximal LAD stenosis only. The absolute survival benefit was found to be greatest in patients with severe three-vessel disease.

Studies comparing CABG and angioplasty in terms of health-related quality of life have not shown differences but this has been largely due to methodological problems in the studies. Indirect assessment of quality of life (via reductions in rates of angina) shows a benefit for CABG over angioplasty.

The relative cost of the two procedures depends on the point of follow-up. The most recent UK cost analysis showed an initial mean cost of angioplasty that was 52% of the cost of CABG, a proportion that increased to 81% at 2 years. No recent cost-effectiveness analyses have been identified, and none at all relating to UK practice. The most recent, undertaken in the USA using non-trial data and requiring caution in interpretation, concluded that angioplasty is likely to be more cost-effective than CABG as long as complete revascularisation is possible, which may not be feasible in patients with three-vessel disease.

Chapter 6

Non-comparative observational studies of CABG only

Introduction

The non-comparative observational studies of CABG, that is, studies reporting results from prospective and retrospective cohorts who underwent CABG are reviewed in this chapter. As with the non-comparative studies of angioplasty, the generalisability of these studies may be limited and they do not allow the relative effectiveness of CABG and angioplasty to be examined. The need for caution when comparing outcomes in observational studies of outcomes of CABG (even after adjustment for case-mix) has been emphasised (Sowden, *et al.,* 1995). It is also clear that observational studies of effectiveness, because of the difficulty in controlling completely for confounding variables, are a poor second-best to RCTs (Sheldon, 1994). However, such studies do allow some examination of the relative effectiveness of CABG in subgroups of patients. Results are summarised from three sources: the RAND and SBU reviews of the effectiveness of CABG, and relevant studies which have been published subsequently.

Clinical effectiveness

The RAND review of the effectiveness of CABG emphasised the results of RCTs, and little observational data were presented on the clinical effectiveness of CABG for chronic stable angina. The inclusion criteria for observational studies were unclear; although observational studies of CABG only appear to have been eligible for inclusion in the review, the results of such studies were not clearly identified and their contribution to the conclusions of the review was unclear. More details relating to the quality of the RAND review appear in appendix 1.

The SBU report found from observational studies that peri-operative mortality and MI were the major risks associated with CABG and that patients from later studies were in a more advanced state of disease than in earlier studies. This was considered to contribute to increases in operative mortality. The other main findings from observational studies of CABG in chronic stable angina were as follows.

- Operative mortality for women is about twice that for men.
- Age is an independent predictor of outcome; for elderly patients operative mortality is high, although late survival and relief of angina are good.
- Impaired left ventricular dysfunction (LVD) is an important risk factor for operative mortality.
- Diabetes and renal insufficiency are risk factors for operative mortality and post-operative complications.
- Obesity increases postoperative length of stay and postoperative complication rates, although not operative mortality.

The impact of smoking on outcomes of CABG was also examined in the 1994 SBU review. Based on subgroup analysis of data from the CASS trial, smoking appeared to reduce 10-year survival. Cox regression analysis of all randomised and randomisable patients showed that the relative risk of death in patients with ejection fractions > 0.5 was 1.6 ($p = 0.002$). Smoking was also found to be an independent predictor of death while awaiting surgery based on the results of a consecutive series of 1124 patients (Suttorp, *et al.,* 1992), emphasising the importance of overall lifestyle change in patients eligible for coronary artery surgery. No data on the impact of smoking on outcomes of PTCA are reported in the SBU review.

A total of 36 prospective or retrospective cohort studies published since the RAND and SBU reviews have been identified which met the inclusion criteria. These are summarised in appendix 8. The size of these studies ranged from the minimum eligible for inclusion (1000 patients) up to more than 172,000 patients; most studies, however, had a sample size of fewer than 3000 patients. The length of follow-up of those patients operated upon varied from those receiving in-hospital follow-up only (nine studies) to those followed-up for 10 years or more (eight studies). It should also be noted that the studies discussed below are North American unless stated otherwise.

Overall results of non-comparative studies, summarised by outcome

In-hospital mortality rates of about 1–3% are reported in the majority of studies examining this outcome. However, one study reported a notably higher rate (7%), possibly associated with greater disease severity and a high prevalence of diabetes among the patients (Weintraub, *et al.,* 1995a).

Long-term mortality was reported by 22 studies. In three studies in which 1-year mortality was reported (Risum, *et al.,* 1995 (Norway); Maddern, *et al.,* 1984 (Australia); Peterson, *et al.,* 1995) mortality rates of 3–8% were cited. In 13 studies 5-year mortality was reported, with mortality at follow-up ranging from 8% to 11% (11 studies). However, one study reported 24% mortality at 5-year follow-up. This same study reported high in-hospital mortality caused by greater disease severity in participants (Weintraub, *et al.,* 1995a).

In eight studies, 10-year mortality was reported, with mortality typically within the range 16–28%. As above, a markedly higher 10-year mortality rate (45%) was reported by one study (Weintraub, *et al.,* 1995a).

One study reported a 20-year mortality of 62% (Rahimtoola, *et al.,* 1993a). A lower 20-year mortality rate of 53% was reported from a Canadian cohort of 1388 patients (Fitzgibbon, *et al.,* 1996). These patients (mostly military personnel) had undergone their first bypass operation at a mean age of 49 years and 12% were aged under 40 years.

One study focused specifically on the association between increasing age and long-term mortality, and examined survival at up to 10 years post-CABG (Canver, *et al.,* 1996). This study is discussed below.

Angina at follow-up was reported by half the studies (n = 16). The prevalence of in-hospital angina was only reported by two studies – 1% and 8%, respectively (Teoh, *et al.,* 1987; King, *et al.,* 1992a). The greater age of patients may be responsible for the higher prevalence reported in the second study. At 1-year follow-up, prevalences ranged from 8% to 24% (Cameron, *et al.,* 1995; Teoh, *et al.,* 1987; Killen, *et al.,* 1982a; b) and at 5-year follow-up prevalences of 43%, 7% and 34% were reported (Killen, *et al.,* 1982a; b; Maddern, *et al.,* 1984 (Australia); Christakis, *et al.,* 1993). The lower prevalence in the second study may be due to younger patients (mean age 44 years in 1971). The validity assessment also indicated several problems with this study (see below).

Prevalence of angina at 5 years varies with type of graft, with a lower prevalence with internal mammary artery (IMA) than non-IMA grafts (Azariades, *et al.,* 1990). Freedom from angina at 5 years was more likely with more than one graft (Bell, *et al.,* 1992).

In-hospital MI was found to be 5% or lower in most studies which reported this outcome. The highest rate (11%) was reported in one 1980 study employing saphenous vein grafts (SVG) (Tyras, *et al.,* 1980), although two more recent studies reporting results for SVG procedures cite rates of about 2% (Acinapura, *et al.,* 1989; 1992.). Long-term MI rates are reported in ten studies, although an overall summary is difficult because of heterogeneity in the presentation of results resulting from variable lengths of follow-up, and variations between studies in reporting of data. However, the MI rate at 5 years is reported to be less than 1.5% per year (Rahimtoola, *et al.,* 1993a; Barner, *et al.,* 1985). At 5 years, rates of 2–6% are reported (Christakis, *et al.,* 1993; Rahimtoola, *et al.,* 1993b; Azariades, *et al.,* 1990), although one study (Bell, *et al.,* 1992) reported a rate of 16% but all patients in this study had three-vessel disease.

Graft patency data is reported in only four studies (Sheldon & Loop, 1984; Barner, *et al.,* 1985; Tyras, *et al.,* 1980; Acinapura, *et al.,* 1992). Again, length of follow-up varies. Three of these studies compare patency of IMA grafts and SVGs, and show that IMA is associated with significantly greater patency at 1 year (96% versus 93%, $p < 0.02$) (Barner, *et al.,* 1985), 4 years (94% versus 90%, $p < 0.01$) (Tyras, *et al.,* 1980), 5 years (88% versus 74%, $p < 0.001$) (Barner, *et al.,* 1985) and, in the most recent study (1992), approximately 8 years (Acinapura, *et al.,* 1982). One study also indicated a total overall patency of 82% at 6 or more years (Sheldon & Loop, 1984).

The need for subsequent revascularisation with angioplasty or CABG is detailed in 14 studies. The need for re-CABG appears to be about 1% per year (Killen, *et al.,* 1982a, b; Rahimtoola, *et al.,* 1993a), with an incidence of re-CABG within the first 5 years of 3–4% (Salomon, *et al.,* 1990; Weintraub, *et al.,* 1995a; Rahimtoola, *et al.,* 1993b).

Details of the quality of the primary studies are summarised in appendix 13. Briefly, there is little heterogeneity among the studies. Three studies, however, scored low on the validity assessment

in terms of representativeness: Peterson and colleagues (1995) because the study population were octogenarians; Mantia and colleagues (1994) and Maddern and colleagues (1984) because there is so little information on the inclusion criteria, or on the baseline characteristics of the included patients, thus making it difficult to judge the representativeness of the sample.

Patient characteristics and comorbidities

The studies discussed above are summarised below in terms of patient characteristics, in order to highlight their effects on treatment outcomes.

Gender Results are broken down by gender in many of these studies, so information on the relative success of CABG in men and women can be derived for most of the outcomes described above. The results show that outcome is generally worse for women, although the absolute differences are often small. For example, all eight studies which give separate data for men and women on in-hospital mortality showed a higher incidence in women (Laird-Meeter, *et al.,* 1987a; b (The Netherlands); Brandup-Wognsen, *et al.,* 1995 (Sweden); Salomon, *et al.,* 1990; Rahimtoola, *et al.,* 1993b; Mickleborough, *et al.,* 1995; Jaglal, *et al.,* 1995; Richardson & Cyrus, 1986; King, *et al.,* 1992a). In most studies, the incidence in women was about twice as high as in men (1–2% for the majority of studies). Longer-term mortality was similarly higher in women. This gender differential appears to persist over time, as it is reported at periods of follow-up of 2, 5, 10, 15 and 18 years. At 2 years, the respective incidences for men and women are 3.8% and 6%, increasing to 58% and 63% at 18 years (Brandup-Wognsen, *et al.,* 1995 (Sweden); Rahimtoola, *et al.,* 1993b; Richardson & Cyrus, 1986).

In-hospital angina at follow-up is higher in women than men (1.3% versus 0.4%) (King, *et al.,* 1992a) and has also been found to be significantly higher in women at 15–20 years (Rahimtoola, *et al.,* 1993a; b). For example, in patients whose angina was categorised as NYHA class IV, prevalence is 12% in women versus 7% in men at 15–18 years (Rahimtoola, *et al.,* 1993b), and 8% versus 5% at 20 years (Rahimtoola, *et al.,* 1993a).

In-hospital and long-term MI rates also differ in this respect. Higher in-hospital rates are reported for women in two studies(3–5% for men, 5–7% for women) (Mickleborough, *et al.,* 1995; King, *et al.,* 1992a), although a slightly higher rate for men was reported in one study (2.4% versus 1.2%) (Richardson & Cyrus, 1986). Both peri-operative and postoperative in-hospital MI rates were reported in one of these studies, both of which were higher in women (King, *et al.,* 1992a). Long-term MI rates were broken down by gender in one study. This showed a small advantage for women at 5 years (6% men, 7% women) which had disappeared at 10 years (16% men versus 15% women) and 15 years of follow-up (28% men versus 26% women) (Rahimtoola, *et al.,* 1993b).

The need for re-intervention was reported in two studies, both of which found a small difference between men and women in need of CABG at 5 years (3% men, 4% women) (Rahimtoola, *et al.,* 1993b) and 10 years (15–16% men versus 16–18% women) (Rahimtoola, *et al.,* 1993a; b). At 15-year follow-up the studies agreed that the need for re-grafting was slightly higher for men (32–34% versus 30–31%).

Age Several studies presented separate results for older and younger patients on the rate of in-hospital mortality. Most commonly these compared the rates in under-65-year-olds to over-65-year-olds. Among the younger group, the incidence of MI was found to be 1–2% (Brandup-Wognsen, *et al.,* 1995 (Sweden); Morris, *et al.,* 1990; Schmuziger, *et al.,* 1994 (Switzerland); Rahimtoola, *et al.,* 1993b; Gersh, *et al.,* 1983). Among those aged over 70 years, the rate was found to be 5–8% (Stahle, *et al.,* 1991 (Sweden); MacManus, *et al.,* 1990; Brandup-Wognsen, *et al.,* 1995; Salomon, *et al.,* 1990), although a higher rate (10%) was found in one study (Cameron, *et al.,* 1995). This study has already been described as involving a high proportion of severely diseased and diabetic patients (Weintraub, *et al.,* 1995a). This outcome was examined separately in one study for patients aged 80 years or more and a rate of 11.5% was found (Peterson, *et al.,* 1995).

Long-term mortality also shows an association with age. At 1–4 years, younger patients appear to have a lower mortality rate. How patients are categorised varies from study to study. However, significant differences in mortality have been found at 1 year when patients aged 70 years and younger are compared with those aged 80 years or more (7.9% versus 19%, $p < 0.001$) (Peterson, *et al.,* 1995), and at 2 years when patients aged under 50 years are compared with those aged over 70 years (1.9% versus 6.1%, $p < 0.001$) (Brandup-Wognsen, *et al.,* 1995, Sweden). Age differences are also found at 3 and 4 years (Peterson, *et al.,* 1995; Morris, *et al.,* 1990).

Longer-term survival is examined in an American study of the association between age and 10-year mortality (Canver, *et al.,* 1996). In this study, mortality in a cohort of 1689 men, most with three-vessel disease, was compared with mortality in a group of age-matched population controls. Patients undergoing repeat CABG were excluded. A linear correlation existed between increasing age and early mortality, and 10-year survival was reduced with increasing age. Survival was greater in the age-matched population controls for patients aged under 70 years. However, no significant survival difference was found for patients aged under 70 years, indicating an acceptable early mortality and long-term survival following CABG in elderly patients.

Separate data on angina at follow-up is only available from one study, which revealed a significant trend associating increased age with angina prevalence (Weintraub, *et al.,* 1995a). None of the studies reported long-term MI rates, need for re-intervention (CABG or angioplasty) or information on graft patency broken down by gender.

Comorbidity: diabetes and hypertension Few of the included studies presented outcome information separately for diabetic patients. However, five studies compared the risk of in-hospital MI in diabetic and non-diabetic patients. The results generally suggest that the risk of in-hospital mortality is about twice as high for diabetic patients compared with non-diabetic patients (2–3% versus 5%) (Stahle, *et al.,* 1991 (Sweden); MacManus, *et al.,* 1990; Morris, *et al.,* 1990), although one Norwegian study found no increase in early mortality associated with diabetes (Risum, *et al.,* 1995; 1996). However, the number of patients with diabetes actually included in the study is small (n = 45). Long-term mortality (4 years) is also higher in patients with diabetes (13% versus 8%) (Morris, *et al.,* 1990). The Norwegian study also confirmed an increase in risk of long-term mortality in diabetics, after adjustment for other risk factors, including number of diseased vessels (RR = 1.87; 95% CI, 1.60–2.14). Only one study reported information on patients with hypertension; the incidence of in-hospital MI was found to be significantly higher in this group (MacManus, *et al.,* 1990).

Disease severity: number of vessels diseased Four studies present in-hospital mortality rates according to the number of diseased vessels. Two of these show rates of about 2% with single-vessel disease, rising to 4% with three-vessel disease (Risum, *et al.,* 1995 (Norway); Brandup-Wognsen, *et al.,* 1995, Sweden). In one study an increase from 0.4% to 1% is shown (Killen, *et al.,* 1982a; b) and, in another, no clear trend (Rahimtoola, *et al.,* 1993b).

A clear association is demonstrated between long-term mortality and number of vessels diseased, with five studies showing a greater mortality in three-vessel disease at 2-, 5- and 10-year follow-up (Laird-Meeter, *et al.,* 1987a; b (The Netherlands); Killen, *et al.,* 1982a; b; Brandup-Wognsen, *et al.,* 1995 (Sweden); Sheldon & Loop, 1984; Morris, *et al.,* 1990). All three studies for which 5-year mortality was reported showed differences between one-vessel and three-vessel disease: 3% versus 10%, 5% versus 11% and 13% versus 15%. Two studies in which outcome at 10 years was reported showed a doubling of mortality in three-vessel compared to single-vessel disease (12% versus 29% and 18% versus 35%) (Laird-Meeter, *et al.,* 1987a; b; Morris, *et al.,* 1990).

Relief of angina at follow-up shows no clear association with number of diseased vessels (Cameron, *et al.,* 1995; Killen, *et al.,* 1982a; b) and for no studies were results reported for in-hospital MI rate or graft patency by number of vessels involved. Long-term MI rates are reported for one study, which showed no differences in rates between groups at 10 years (Killen, *et al.,* 1982a; b). For one study the need for re-intervention is reported; this showed the need for re-CABG to be slightly greater in those with three-vessel disease compared with those with one- or two-vessel disease (1% versus 2%) (Killen, *et al.,* 1982a; b).

Ejection fraction In-hospital mortality is reported according to ejection fraction in six studies, and the results indicate that preoperative ejection fraction is a key determinant of outcome. An ejection fraction of less than 40% is associated with at least a doubling of risk of death compared with one greater than 40% (Teoh, *et al.,* 1987; MacManus, *et al.,* 1990; Morris, *et al.,* 1990; Schmuziger, *et al.,* 1994 (Switzerland)), or greater than 60% (Risum, *et al.,* 1995 (Norway); Brandup-Wognsen, *et al.,* 1995 (Sweden); Salomon, *et al.,* 1990). Results from one study indicate that this increase is evident whether the graft is a first operation or a reoperation (Salomon, *et al.,* 1990). The same increase in risk also applies to long-term mortality on the evidence of three studies presenting this information. The earliest study, from 1984 to 1987, presents this outcome according to 'normal' and 'poor' ejection fractions, and reports a 10-year mortality of 12% in patients with poor initial ejection fraction compared with 5% in those with normal ejection fraction (Laird-Meeter, *et al.,* 1987a; b (The Netherlands)). The other two studies

report that mortality is twice as high in those with ejection fractions less than 40% compared to those with a higher levels, at both 2 and 4 years. For example, at 2 years mortality is 8% in those with ejection fractions less than 40% compared with 3.6% with ejection fractions greater than 60% (Brandup-Wognsen, *et al.,* 1995, Sweden).

Angina at follow-up also appears to show a clear relationship with ejection fraction, although data are reported in only one study. This shows that about 7–8% of patients with ejection fractions less than 40% followed-up in-hospital have angina post-CABG, compared with 11–12% of those with ejection fractions greater than 40% (Teoh, *et al.,* 1987). Information on angina at longer periods of follow-up is not available from these registry studies. One study reported that the risk of in-hospital MI increases significantly with decreasing ejection fraction (Christakis, *et al.,* 1992). The same information is not available for long-term MI, graft patency or need for re-intervention (CABG or angioplasty).

NYHA angina category A similar pattern of results might be expected for NYHA angina categories as is described for other measures of initial disease severity, and this is indeed the case. All studies reporting in-hospital mortality show that the risk is at least twice as high in category IV (6–13%) as in category III (2–3%) (Teoh, *et al.,* 1987; Stahle, *et al.,* 1991 (Sweden); Risum, *et al.,* 1995, Norway). One study reported that the risk was about four times greater in categories III and IV combined, compared with categories I and II (Schmuziger, *et al.,* 1994, Switzerland). Long-term mortality rates are not reported in these studies according to NYHA class, although information on prevalence of angina at follow-up periods ranging from in-hospital to 20 years is presented. This indicates that the likelihood of remaining angina-free at follow-up decreases with increasing NYHA class (Teoh, *et al.,* 1987; Rahimtoola, *et al.,* 1993a; Schmuziger, *et al.,* 1994 (Switzerland); Rahimtoola, *et al.,* 1993b; Azariades, *et al.,* 1990). No relevant results on rates of in-hospital and long-term MI are available. Similarly, no information on graft patency or need for re-intervention is presented.

Left main artery disease Separate information on patients with left main artery disease is presented in four studies. Two studies are in agreement that involvement of this artery doubles the risk of in-hospital MI from 3% to 5–6% (Risum, *et al.,* 1995 (Norway); Brandup-Wognsen, *et al.,* 1995 (Sweden)). Mortality is higher at 2 years compared to patients without left main artery involvement (5.2% versus 4%) (Brandup-Wognsen, *et al.,* 1995), and also at 5 and 10 years (5 years: 15% versus 11%; 10 years: 26% versus 23%) (Sheldon & Loop, 1984).

Left ventricular dysfunction Only one study examined this and found that in-hospital mortality was higher in those with LVD (Rahimtoola, *et al.,* 1993b). This finding applied to both men and women.

Type of procedure: SVG versus IMA Five studies from the 1980s and early 1990s were identified in which comparisons of different types of graft were reported. Four of these examined in-hospital mortality and found a slightly higher risk with SVGs compared with IMA, although the differences were not significant. In one study a much lower risk of in-hospital mortality was found with IMA than with non-IMA grafts (2.8% versus 7.6%, $p = 0.003$) (Azariades, *et al.,* 1990). Long-term mortality (9 years) has also been found to be significantly lower with IMA than with SVG (Acinapura, *et al.,* 1989; 1992), although one study found no difference at 5 years (Tyras, *et al.,* 1980).

Angina at follow-up has been found to be higher in patients receiving an SVG compared with an IMA graft (15–18% IMA versus 31% SVG; follow-up period 9 years) (Acinapura, *et al.,* 1989; 1992). However, in one study no difference was found in angina prevalence at approximately 4 years. The patients in this latter study were younger (mean age 53 years) than in the two previously cited studies (mean ages 66 and 63 years, respectively). In another study comparing IMA with non-IMA grafts, no clear pattern emerged in older patients (over 70 years) after 5 years (Azariades, *et al.,* 1990).

In-hospital MI was found in two studies to be similar for IMA and SVG (Acinapura, *et al.,* 1989; 1992). MI rates for IMA and non-IMA grafts do not differ in another study (Schmuziger, *et al.,* 1994, Switzerland). However, the authors of one study report an almost doubling of risk of MI with SVG; this discrepant result may be explained by the significantly higher prevalence of left main stenosis in the group receiving SVG (Tyras, *et al.,* 1980). Long-term MI appears to be more common in the SVG group (Tyras, *et al.,* 1980; Azariades, *et al.,* 1990), with a significantly higher rate (2.3% versus 5.2%, $p < 0.05$) reported in one study at approximately 4 years follow-up (Tyras, *et al.,* 1980).

In three studies which examined graft patency, significantly higher graft patency was found with SVG (Barner, *et al.,* 1985; Tyras, *et al.,* 1980; Acinapura,

et al., 1992). This difference was found after 1 year (e.g. 96% versus 93%, $p < 0.02$) (Barner, *et al.,* 1985) and after a mean of 8.5 years of follow-up (96% versus 70%, $p < 0.001$) (Acinapura, *et al.,* 1992).

The need for re-intervention was examined in three studies. In two a much higher risk of subsequent CABG or angioplasty in the SVG group was reported at approximately 9 years follow-up (1% IMA versus 6–10% SVG, $p < 0.05$) (Acinapura, *et al.,* 1989; 1992). However, no difference between IMA and non-IMA grafts at 5 years was reported by one study in an older group of patients (aged over 70 years) (Azariades, *et al.,* 1990).

Number of grafts Outcomes according to the number of grafts carried out were examined in three studies. Two of these found freedom from angina at follow-up to be more likely with multiple grafts at 6- and 10-year follow-up (Bell, *et al.,* 1992; Killen, *et al.,* 1982a; b). Multiple grafts were also associated with less need for re-intervention and less risk of long-term MI (Killen, *et al.,* 1982a; b). In the remaining study, however, no benefit was found from multiple versus single IMA grafting (Schmuziger, *et al.,* 1994, Switzerland).

First operation versus reoperation Patients receiving a second CABG have been compared with those receiving their first CABG in five studies. In-hospital mortality appears to be much higher with reoperations, with a rate of 2–3% in 'first CABG' patients compared with 5% or greater for reoperations (Teoh, *et al.,* 1987; Stahle, *et al.,* 1991 (Sweden); Sheldon & Loop, 1984; Schmuziger, *et al.,* 1994 (Switzerland); Salomon, *et al.,* 1990). Mortality at 5 and 10 years are also greater with reoperations (19% versus 11%; 35% versus 26%, $p < 0.001$) (Salomon, *et al.,* 1990). The risk of in-hospital MI is similar (Sheldon & Loop, 1984; Schmuziger, *et al.,* 1994).

Completeness of revascularisation is examined in one multicentre cohort study of almost 3000 patients (Jones & Weintraub, 1996). Long-term prognosis was found to be better with complete revascularisation across a range of outcomes including 10-year mortality and recurrent angina. Incomplete revascularisation was significantly associated with death at follow-up at a mean of 12 years, after controlling for baseline differences in the two groups.

Endartectomy plus CABG was compared in one study with CABG alone; no differences were found between them in terms of long-term mortality or in-hospital MI (Christakis, *et al.,* 1993).

Year of procedure There is little clear evidence of any changes in outcome of CABG over time. Better outcomes might be expected in more recent studies with increasing experience of the procedures and improved management of patients. Worse outcomes might be expected if older and more severely ill patients are more likely to be treated, as in recent years. For example, the SBU review found that operative mortality from CABG increased between 1981 and 1987. In the current review, however, few outcomes were reported consistently in a large enough range of studies to allow these issues to be explored. The most commonly reported outcome, in-hospital mortality, appears in ten studies and, for patients over 65 years of age, there is an increase with time. However, there is great heterogeneity among the studies. A similar pattern exists for patients aged under 65 years. If this is a true effect, it is likely to be caused by the increasing disease severity of the patients being operated upon, as was also found by the SBU reviewers. Despite the increasing severity of cases, however, 5-year survival has remained steady at around 90% or more since the studies published in the early 1980s.

Smoking At the time when the main literature search for this review was conducted, no new studies on the impact of smoking were found which met the inclusion criteria. The CASS study discussed earlier had shown a decrease in 10-year survival and higher rates of recurrence of angina in smokers, and this decreased survival in smokers is also found in a Swedish study of 4661 patients undergoing their first isolated CABG (Cameron, *et al.,* 1995; Stahle, *et al.,* 1994). Although several other observational studies have also been recently published, none met the inclusion criteria for this review because their sample sizes were small. This has made this issue difficult to explore fully.

Other observational studies which did not meet the inclusion criteria because of their size have also been published and, for completeness, they are worth summarising briefly. Of 11 studies with sample sizes between 200 and 1000 (the cut-off point for inclusion in this review), nine found that smoking increases the risk of early and late mortality, MI, need for reoperation and angina (Voors, *et al.,* 1996, 1997; Boucher, *et al.,* 1997; Christakis, *et al.,* 1996; van Brussel, *et al.,* 1995; Ranger, *et al.,* 1996; He, *et al.,* 1994; Ramstrom, *et al.,* 1993a; b). One study of 349 patients found no effect of smoking on re-occlusion (Cataldo, *et al.,* 1993) and one study of 262 patients reported no effect on 3-year graft patency (Goldman, *et al.,* 1997). However, since the main literature search

was completed, one study of 2916 patients having their first CABG found that smoking did not predict mortality or morbidity (Utley, *et al.,* 1996). The groups were otherwise similar in baseline characteristics. Overall, however, there appears to be increasing evidence that outcomes of CABG are worse in smokers, underlining the importance of smoking cessation in these patients. (Note: The smaller studies and the recent large prospective study have not been reviewed in detail but have been included retrospectively as most of the observational studies in this area which met the inclusion criteria did not report subgroup analyses of the impact of smoking.)

Generalisability The results of the subgroup analyses confirm the earlier results of the SBU review. Operative mortality is confirmed as being about twice as high for women as men, and in-hospital mortality is higher in older age groups. Impaired LVD was only examined in one new study but this confirmed that it is a risk factor for in-hospital mortality. Diabetes also was found in both reviews to increase the risk of in-hospital mortality. No new studies meeting the inclusion criteria were found which examined the effect on outcome of obesity or renal insufficiency.

Health-related quality of life

Eleven prospective studies have been identified which focus on the implications of CABG for patients' health-related quality of life, and these are summarised in appendix 8. These studies are of series of patients admitted to one or more centres. Three of them are UK-based. The studies by Mayou and Bryant (1987; Bryant & Mayou, 1989) (n = 79) and Caine and colleagues (1991) (n = 100) both report outcomes at 1-year follow-up for patients with a mean age of just over 50 years. However, the latter study is of a superior quality methodologically, with more explicit inclusion criteria and less apparent heterogeneity among the sample of patients. Both these studies, however, agree that there is some improvement in psychological morbidity long term. The latter study indicated that not only were postoperative NHP scores improved compared with preoperative levels but were now comparable to age-matched male population norms. Improvements in social life were also noted. Caine and colleagues, but not Mayou and Bryant, noted significant improvements in work-related and sexual functioning. This difference may be related to differences in baseline characteristics of the cohorts under study but it is difficult to determine whether the patients in the two studies are comparable. A similar proportion of both groups had received three or more bypass grafts (about 84%) and 77% of Caine and colleagues' group of patients had three-vessel disease although, in the latter case, little other baseline information is given. The Mayou and Bryant study also found that a significant minority were dissatisfied with their general level of recovery.

In the only other UK study in this group, outcomes were reported for an older group of 145 patients undergoing CABG – 62% were men, 28% had a previous MI and 6% had poor LVF. At a mean length of follow-up of 5 months, it appeared that most patients experienced improvements in their health-related quality of life, in terms of reduced disability and distress, although about a third of patients experienced no improvement (Kallis, *et al.,* 1993).

Three other European studies were identified. In Sweden, Sjoland and colleagues (1996) used a prospective series of CABG patients to assess the impact of the procedure on health-related quality of life using the NHP, the PGWB index and a physical activity scale. With baseline measurements on 245 patients and follow-up measurements on 327 at 2-year follow-up, the study demonstrated statistically significant improvements in NHP scores on all dimensions except isolation, the physical activity score and the PGWB index. Greatest improvements were seen in patients with the greatest impairment to exercise capacity, with more severe angina and in women.

In a Norwegian study, 213 patients (89% male, mean age 61 years) admitted for CABG were followed for 1 year (Steine, *et al.,* 1996). Most (94%) of these were in NYHA angina classes II and III before surgery, compared with 78% in class I after surgery. Other benefits of surgery included improvements in psychological functioning (based on General Health Questionnaire scores) in two-thirds of patients. There was no significant gender difference found in improvement in well-being.

The Spanish study by Permanyer-Miralda and colleagues (1991) was cross-sectional in design, in that it compared two groups of male patients, one of whom had undergone CABG 6 months previously (n = 45). The comparison group was patients with stable angina admitted for angiography (n = 48). However, the purpose of the study was not comparative but to examine associations between functional status and self-perceived health status and little can be said about the effect of CABG on health-related quality of life

based on these results. Moreover, in terms of the quality of the study, there are few details of inclusion criteria or baseline information on the included patients and it is not clear that the patients were enrolled at a similar stage of illness.

Significant improvements in psychological, social, sexual and physical functioning were also reported from an Australian prospective study of 89 patients of mean age 56 years (Langeluddecke, *et al.,* 1989). Most of the participants had three- or more vessels diseased. This study also asked patients for a subjective evaluation of surgery and found 5% regretted having it. Three of the four American studies which report on long-term health-related quality of life in CABG patients also report significant improvements in psychological and physical functioning, life satisfaction and health perception (Flynn, *et al.,* 1987; Gold, *et al.,* 1995; King, *et al.,* 1992b). However, Klonoff and colleagues (1989), in the fourth of the studies from the USA, found no long-term impact of CABG on intellectual or neuropsychological functioning. King and colleagues (1992b) specifically asked patients whether surgery had been 'worth it'; 15% were not sure, or did not think it was worth it. This was related to angina severity and functional disruption at 1 year.

The study designs described above (with the exceptions noted) have been quality assessed using a standard checklist and most are of acceptable quality – that is are without major methodological flaws likely to undermine their conclusions (see appendix 13). The quality of the health-related quality of life instruments used is shown in appendix 13, according to whether they have been reviewed in Bowling (1991; 1995). However, one study (King, *et al.,* 1992b) has a particular methodological problem which may affect its generalisability; it presents very little information on both the baseline characteristics of patients and the inclusion criteria.

Cost and cost-effectiveness

Given that most good quality economic analysis is comparative in nature, it is not surprising that only one economic study focusing on CABG and fulfilling the inclusion criteria of this review has been located in the literature. Dougenis and colleagues (1992) undertook a retrospective cost comparison of initial and repeat CABG (see appendix 8). The authors found that repeat CABG was 1.8 times as costly as the initial procedure. Only hospital costs were included in the analysis, and resource use data were taken from only 15 patients for initial CABG and from five patients for the repeat procedure. The study was not of a high quality (see appendix 13) and, despite being one of the few economic studies undertaken within the UK, is likely to be of limited value to NHS decision-makers.

Conclusions

CABG relieves angina in the large majority of patients undergoing surgery and it further appears that IMA grafts are associated with greater long-term patency and less angina at long-term follow-up than non-IMA grafts. The need for re-CABG is about 1% per year. Many outcomes of surgery appear to be slightly worse for women than men and for older patients; for example, relief of angina and long-term mortality are both age-related. Short- and longer-term mortality also show a clear association with disease severity (number of vessels diseased), ejection fraction and initial severity of angina.

Along with improvements in functional status, CABG also brings improvements in health-related quality of life; physical, sexual and social functioning improve significantly in the large majority of patients. A minority of patients, however, may remain dissatisfied with the outcome of surgery. This appears to be related partly to remaining disability (King, *et al.,* 1992b) and partly to heightened expectations as to what they would be able to achieve as a result of surgery (Mayou & Bryant, 1987).

No published economic analyses were found that are likely to be helpful to decision-makers in the NHS.

Chapter 7

Use of medical adjuncts to CABG

Introduction

There is no information on medications used as adjuncts to CABG in the RAND and SBU reviews. However, there is some information available from the Antiplatelet Trialists' Collaboration review (1994a; b) on the effectiveness of antiplatelet therapies in preventing long-term outcomes (death, MI, and stroke) in patients post-CABG. The mean duration of treatment for patients in this high risk subgroup was 16 months, and the meta-analysis showed a trend in favour of antiplatelet agents, although this was not significant.

The second part of the Antiplatelet Trialists' Collaboration review aimed to determine the efficacy of antiplatelet therapy in maintaining vascular patency in various categories of patient, including patients undergoing CABG or angioplasty (Antiplatelet Trialists' Collaboration, 1994b). When combining all events, antiplatelet therapy produced a substantial reduction in vascular occlusion rates. For coronary artery grafts the odds of occlusion reduced from 30% (control) to 21% (antiplatelet group), benefiting 90 patients per 1000 treated for 7 months.

For the current review, seven RCTs were found which met the inclusion criteria and in which the effect of adjunctive medical therapy in coronary bypass patients was examined. These studies are summarised in detail in appendix 9. The treatments administered included aspirin with and without dipyridamole, warfarin and beta-blockers, with follow-up ranging from in-hospital only to almost 7 years. A heterogeneous range of outcomes was assessed:

- in-hospital mortality – 1 study
- long-term mortality – four studies
- angina at follow-up – two studies
- graft patency – four studies.

The results are summarised below according to treatment group.

Clinical effectiveness

Aspirin with or without dipyridamole versus placebo or control

Two studies compared aspirin with or without dipyridamole with a control group. Brown and colleagues (1985) randomised 147 patients to aspirin, 325 mg three times daily, aspirin plus dipyridamole, 75 mg three times daily, or placebo. Patients were followed-up after 1 year and the main outcome, graft patency, was assessed. Multivariate analyses indicated that both aspirin and aspirin plus dipyridamole were significantly associated with lower occlusion rates after controlling for a range of traditional coronary risk factors and other variables. Timing of treatment was also important – occlusion was less common among patients receiving treatment on the first postoperative day than among those receiving it on the third day. The difference in occlusion rates with therapy was translated into clinical benefit for the patient; those with fewer occluded grafts were significantly less likely to report pain during exercise testing at follow-up. However, the addition of dipyridamole to aspirin did not appear to increase effectiveness of treatment. Compliance was assessed with pill counts, urine salicylate measurement and bleeding time measurements.

A good quality RCT (double-blind, with intention-to-treat analysis and relatively complete follow-up) of 948 patients undergoing SVG has shown occlusion rates to be lower with aspirin plus dipyridamole than with aspirin alone. There was some evidence of an increase in clinical events in the group receiving combination therapy (RR, 1.46; 95% CI, 1.02–2.08) (van der Meer, *et al.*, 1993).

Mayer and colleagues (1981) also reported graft patency data for patients receiving aspirin, 1300 mg daily, and dipyridamole, 100 mg daily, following left IMA or SVG. Both groups received a similar number of grafts per patient (mean 1.9). At 3–6 months follow-up, overall patency was significantly higher in the treatment group than in controls receiving no treatment (94% versus 82%, $p < 0.02$). Graft patency with treatment was more common for men than for women, although numbers in subgroups were small. The benefit of treatment was maintained when results were broken down by type of graft used. Although compliance with therapy was assessed no information is presented.

Aspirin versus warfarin

McEnany and colleagues (1982) studied 216 patients who had received between one

and four SVGs and were allocated to either aspirin, 300 mg twice daily, warfarin (dose not stated), or placebo. Graft patency was significantly higher at 1-year follow-up in the warfarin group than in the aspirin group, and higher in both groups than in placebo. Angina prevalence at follow-up was also lower in the warfarin group than in the aspirin group ($p < 0.01$).

Aspirin plus dipyridamole plus warfarin

Gershlick and colleagues (1988) allocated patients to receive either aspirin, 330 mg three times daily, plus dipyridamole, 75 mg three times daily, plus warfarin, or placebo plus warfarin. Treatment was continued for a mean of 25 months. All patients received warfarin for a mean of 3.2 months postoperatively. At a mean follow-up of 6.6 years, aspirin plus dipyridamole was found to confer no significant benefit in terms of number of cardiac deaths, recurrent angina, MI, exercise test, need for repeat angiography for symptoms or need for reoperation.

Rajah and colleagues (1985) randomised 125 CABG patients to either aspirin, 330 mg three times daily, plus dipyridamole, 75 mg three times daily, plus warfarin, or placebo plus warfarin. All patients were given warfarin for 3 months. The main outcome was graft patency rate, which was significantly higher in the treatment group than in the placebo group (92% versus 75%, $p < 0.01$). Intraoperative blood loss did not differ between groups.

The RCT by van der Meer and colleagues (1993) described above also compared warfarin with aspirin and aspirin plus dipyridamole in an open trial. Outcomes of warfarin therapy are not summarised in detail in this study but warfarin seems to have been as effective as aspirin in preventing re-occlusion, although major bleeding occurred more often with anticoagulant treatment.

Beta-blockers

Two different regimens involving propranolol administration were compared in one study, to determine whether the incidence of clinically important supraventricular tachyarrhythmias could be reduced after CABG (Myhre, *et al.,* 1984). One group of patients scheduled to undergo coronary bypass surgery received routine treatment of propranolol until 12 hours before surgery, while the treatment group received propranolol until 2 hours before surgery and then 20 mg 6-hourly for 8 days. Patients were followed-up for 8 days. There appeared to be no difference in effectiveness between the two groups.

Oka and colleagues (1980) carried out a similar study which randomised 71 patients to receive either propranolol until 48 or 10 hours before surgery, propranolol continued until 36–48 hours after surgery, or no propranolol. In-hospital follow-up suggested that there were differences in MI rate between groups, although the numbers were very small. The main finding was that a rebound effect in sympathomimetic activity appeared to be associated with abrupt propranolol withdrawal before surgery.

Quality assessment of included trials

The overall quality of these RCTs was not high. In particular, it was not clear that, in most of the trials, randomisation had actually resulted in comparable treatment and control groups. Two studies, however, do appear to be of good quality. One of these reported greater graft patency with aspirin plus dipyridamole (Rajah, *et al.,* 1985). The other found warfarin to result in greater graft patency than aspirin (McEnany, *et al.,* 1982).

One meta-analysis is of interest in this section. Kowey and colleagues (1992) undertook a meta-analysis of the effectiveness of medical prophylaxis of supraventricular arrhythmia after CABG. The included trials involved treatments with beta-blockers, digitalis or a combination of these. The analysis of 12 trials showed a significantly reduced incidence of arrhythmia after surgery with beta-blockers and with combination therapy but not for digitalis alone. However, no longer-term outcomes were studied and the methodological quality of the review is quite low, with no details of search or inclusion criteria and no details of the individual trials.

Finally, lipid-lowering therapy (colestipol/niacin) has been found to reduce long-term progression of atherosclerosis, risk of non-fatal MI, cardiac death and need for revascularisation compared with placebo in CABG patients (Azen, *et al.,* 1996).

Health-related quality of life

No studies relating to health-related quality of life were found that fulfilled the inclusion criteria.

Cost and cost-effectiveness

No cost or cost-effectiveness studies were found that fulfilled the inclusion criteria.

Conclusions

Aspirin significantly reduces the odds of occlusion after CABG. There appears to be little difference in effectiveness between aspirin and warfarin, although warfarin may result in greater bleeding. No health-related quality of life or economic studies were found in the literature.

Chapter 8

Non-comparative observational studies of PTCA only

Introduction

The empirical literature relating to angioplasty alone is focused on in this chapter of the systematic review.

Clinical effectiveness

Given the limited comparative data available that were available when they were undertaken, the RAND and SBU reviews of the effectiveness of angioplasty were forced to rely heavily on observational data, which constituted over 90% of published empirical literature (Hilborne, *et al.,* 1991). Some of main points coming out of these reviews of this literature are detailed below (Hilbourne, *et al.,* 1991; Goodman, 1992).

- The rate of major in-hospital complications was estimated as 0.4% for procedural mortality, 3.4% for non-fatal MI and 3.3% for emergency CABG.
- The primary success rate – variably defined but generally relating to successful revascularisations in patients with stable angina – was estimated at 85% and found to be related to number of vessels, degree of stenosis, size of lesion, LVF, duration of angina, age and gender.
- The major limitation of angioplasty is restenosis, which is also subject to variable definition. When associated with symptoms, it was estimated to occur in 25–40% of lesions.
- Long-term MI rates in patients were variably reported as 0–7.1%.
- Repeat angioplasty was found to be required in 21–38% of patients within 5 years of the initial procedure.
- CABG rates after initial angioplasty were found to be 10–15% at 1 year, 19% within 3 years and 14–25% within 5 years.

Since the RAND and SBU reviews, a large number of observational studies have been published on angioplasty. The majority have not been included in this systematic review because their sample sizes do not meet the inclusion criteria (i.e. at least 1000 patients for observational studies).

Twenty studies published since the earlier reviews have been identified which focus on the description of the outcomes of a series of patients undergoing angioplasty. These studies are summarised in appendix 10. As with the observational studies of CABG alone discussed in chapter 6, the main value of these studies of PTCA is to assess the effectiveness of the procedure in specific subgroups.

The first subgroup comparison that is feasible on the basis of the observational data on angioplasty in appendix 10 is between men and women. The RAND review reports evidence from the National Heart, Lung and Blood Institute (NHLBI) registry that shows poorer short-term results in women but better longer-term results, such as restenosis rates, additional revascularisation rates and survival. Since the earlier reviews, six large observational studies focusing on gender differences in outcomes from angioplasty have been identified in the search (Weintraub, *et al.,* 1994; McEniery, *et al.,* 1987; Kelsey, *et al.,* 1993; Bell, *et al.,* 1993; 1995; Arnold, *et al.,* 1994; Topol, *et al.,* 1993a). In general, the results of these studies confirm the data reported in the RAND review – an increased rate of in-hospital mortality and MI in women but with these outcomes very similar subsequent to hospitalisation. Two of the studies indicate higher rates of angina in women at follow-up (Weintraub, *et al.,* 1994; Kelsey, *et al.,* 1993). Re-intervention rates are very similar in men and women. Inevitably, there are likely to be significant differences in case-mix in these studies to explain gender differences.

The second subgroup comparison evident in the observational studies summarised in appendix 10 relates to age at initial revascularisation. The RAND and SBU reviews identify age as one predictor of primary success from angioplasty. However, the early evidence indicated success rates in older patients comparable to those in younger patients. Three observational studies looking at the effect of age on the outcomes of angioplasty have been published since the earlier reviews and are summarised in appendix 10 (Lindsay, *et al.,* 1994b; Richardson, *et al.,* 1994; Thompson, *et al.,* 1993). These studies indicate that in-hospital mortality and MI

rates are higher in older patients but provide no clear evidence about longer-term outcomes.

The RAND and SBU reports review studies which show that a range of other factors will influence prognosis after angioplasty. These include an ejection fraction of greater than 50%, a history of MI, previous CABG, diabetes, hypertension and congestive heart failure. Several recent large observational studies which consider other forms of subgroup analysis relating to angioplasty are also summarised in appendix 10. Stevens and colleagues (1991) looked at the effect of left ventricular dysfunction on prognosis after angioplasty and, despite showing poorer short-term outcomes, concluded that PTCA can be effective in patients with left ventricular dysfunction. Weintraub and colleagues (1993a) attempted to identify risk factors for restenosis and, in multi-vessel disease, found that a higher class of angina, the diameter of stenosis pre-angioplasty and diabetes were the most significant risk factors for restenosis. The number of vessels diseased has also been found to be correlated with short-term outcomes such as in-hospital mortality, need for CABG and non-fatal MI in a large (12,232 admissions from 1989 to 1993) registry study in the USA (Malenka, 1996).

Stein and colleagues (1995) showed a worse prognosis for diabetics after angioplasty, on the basis of short- and long-term outcomes. Scott and colleagues (1994) found few differences between white and black patients relating to the outcomes of angioplasty. Hartzler and colleagues (1988) looked at outcomes from PTCA in patients with a range of possible risk factors and concluded that patient management should be individualised.

The impact of smoking on the outcome of PTCA was not considered in the SBU review, as no relevant observational studies had been identified. There was little information on this subject in the more recent observational studies which met the review inclusion criteria; even when baseline details on the proportion of smokers in the study were included, the authors tended to treat this factor as a confounding variable and then adjusted for it in subsequent multivariate analyses. The most relevant study was identified out of the context of this systematic review, and after the main review was finished.

The authors of this study, which was based on a follow-up period of up to 16 years of > 4000 patients undergoing angioplasty between 1979 and 1995, found that persistent smokers (those who smoked both before and after the operation) had a significantly increased mortality (RR, 1.76; 95% CI, 1.37–2.26) and Q-wave infarction (RR, 2.1; 95% CI, 1.16–3.72) (Hasdai, *et al.,* 1997). Mortality rates were also higher among persistent smokers than among those who had quit, emphasising again the importance of smoking cessation in patients about to undergo angioplasty.

Health-related quality of life

The focus of the review of patient-based outcomes from PTCA in the RAND and SBU reviews was on patients' functional status, particularly in relation to returning to work. The key points from this review are detailed below.

- Among those patients in full- or part-time employment before the procedure, return-to-work rates were 80–100%.
- However, few patients who had left work before their angioplasty were able to return as a result of the procedure.
- Important predictors of a successful return to work after angioplasty were reported as absence of chest pain at follow-up, being male, being older, absence of MI during or before angioplasty, higher education and being a professional or clerical worker. Patients' confidence was also found to affect return-to-work rates.

Since the earlier reviews, three studies have been located in which the quality-of-life implications of angioplasty have been assesses. These studies are summarised in appendix 10. The small sample sizes and absence of clear evaluative questions in the studies by Englehart (1993) and Gulanick and Naito (1994) limit the value of these studies.

The study by McKenna and colleagues (1994) involved an assessment of the improvement in health-related quality of life among 209 patients, mostly with single-vessel involvement and NYHA class I and II angina, who were recruited pre-PTCA. Patients who had previously undergone CABG were excluded and data were collected at a mean of 11 months follow-up. This showed that quality of life, as measured by symptomatic status, functional capacity, psychological well-being, life satisfaction and return to work, improved at short-term follow-up (2 months), with this improvement being maintained at 11 months. A minority of patients (5%), however, were unsure that angioplasty had been of any benefit to them. The study is assessed as being of good quality, based on the criteria already described.

Cost and cost-effectiveness

No cost or cost-effectiveness studies were found that fulfilled the inclusion criteria.

Conclusions

There is some evidence of gender differences in short-term outcomes of angioplasty (e.g. in-hospital mortality and MI) and in rates of angina at longer-term follow-up. Success of PTCA is also influenced by the age of the patient and angina class. Although LVD is associated with poor outcomes, PTCA can still be effective in these patients. Health-related quality of life has been shown to improve after PTCA, as a result of improvements in work status and physical and psychological function, but no information is available on key subgroups in this regard. No economic studies were found in the literature.

Chapter 9

Non-medical adjuncts to PTCA

Introduction

The problem of restenosis following angioplasty has led to the development of several procedural adjuncts to PTCA. At the time of the RAND and SBU reviews these technologies had been subject to only very limited evaluation, based largely on small observational studies. Since then, some RCTs have been undertaken to assess their incremental effectiveness over standard angioplasty.

Clinical effectiveness

Intracoronary stents

A major development in coronary angioplasty has been the use of intracoronary stents which act as scaffolding within the revascularised vessel. Stents have become an important treatment for abrupt vessel closure (Bittl, 1996) but, for the purposes of this review, it is their role as an adjunct to standard PTCA which is of interest. The full results of the RCTs which have been published to date on the use of stents are summarised in appendix 11 (Macaya, *et al.,* 1996; Fischman, *et al.,* 1994; Sirnes, *et al.,* 1996; Versaci, *et al.,* 1997). The results of these studies suggest that, for patients aged 60 years or under with *de novo* lesions, although the incidence of deaths and non-fatal MIs is similar in the stent and standard PTCA groups, Palmaz-Schatz stents seem to reduce the need for subsequent revascularisation procedures.

Based on the results of a meta-analysis by Sanderson (1996), pooled data from the first two trials demonstrate a 33% (4–53%) reduction in repeat PTCA, a 29% (2–48%) reduction in all revascularisations and a trend suggesting a 25% (1–41%) increase in event-free survival. It should also be noted that, although the pooled effect sizes from this meta-analysis are relatively large, the confidence intervals are wide, and, therefore, include apparent benefits of treatment which are likely to be of little clinical significance (e.g. 1%, 2%, 4%).

A further Swedish trial of the additional use of stents in angioplasty has also shown that stenting reduces the incidence of angina, restenosis and re-occlusion rates at 6 months. Most patients had single-vessel disease and, as above, were no more than 60 years old. However, the patient population in this study differed from the previously discussed trials in that all the patients had chronic occlusion (Sirnes, *et al.,* 1996). It is unclear whether assessment of outcomes was blinded.

The results of the above meta-analysis are, however, not supported by a systematic review which has examined the above trials in detail (Savoie & Sheps, 1996). This review found that there was no improvement in health outcomes resulting from the adjunctive use of stents in elective treatment of coronary artery disease, and that the authors of included studies found significant harms (deaths, vascular complications and recurrent symptomatic closures) were associated with the use of stents. In particular, the reduced rate of revascularisation observed in the Belgian and Netherlands stent (BENESTENT) trial was considered to be undermined by the lack of blinding of the investigators to treatment allocation. Savoie and Sheps point out that, given the lack of differences in evidence of ischaemia between the two groups, either in terms of symptoms, ECG or scintigraphic evidence, the investigators may have unintentionally performed more revascularisations in angioplasty patients with ischaemic symptoms than in comparable stent patients; this was subsequently recognised by the authors of the BENESTENT study.

Savoie and Sheps (1996) also highlighted the lack of evidence from both these trials for a reduction in restenosis rates with stents. No difference between stents and PTCA alone was found in the BENESTENT study when baseline reference diameter was used to assess restenosis and, in the Stent Restenosis Study (STRESS), when the results were reanalysed on an intention-to-treat basis, again no differences in restenosis rates were evident. In the latter case, the high dropout rate among patients receiving PTCA was highlighted; this is less likely to be symptomatic, implying that those who were actually followed-up were the more severe cases. This would have the effect of overestimating the restenosis associated with PTCA. Moreover, the difference between patient groups was of borderline statistical significant ($p = 0.046$) and, given the biases referred to above, there seems to be little firm evidence of a difference in

restenosis rates. However, the need for repeat PTCA was significantly reduced by the use of stents.

The review concluded that definite conclusions regarding the effectiveness of elective stenting await longer studies, as the existing trials are becoming rapidly outdated because stent and angioplasty technologies have changed since most of the trial data were collected. A trial published since this review was completed has examined the role of primary stenting in patients with isolated stenosis of the proximal LAD coronary artery (Versaci, *et al.,* 1997). Stenting was associated at 12-month follow-up with a lower rate of restenosis and lower rates of recurrence of angina. No differences in rates of MI or cardiac-related mortality were found, although the study was small. Moreover, as the outcome assessment does not appear to have been systematic and was not blinded to treatment allocation, the trial does not provide any clear evidence that stenting is beneficial.

Two observational studies provide information on stenting outside the context of RCTs. Although not trials, the data from these studies are valuable as they may be more representative of current practice. One is a large French prospective study (Karrillon, *et al.,* 1996). In this registry study 2900 patients were followed-up for 1 month. Patients received aspirin, 100 mg daily, and ticlopidine, 250 mg daily. Coumarin anticoagulation was not used. The majority (97.1%) of patients had an event-free outcome at follow-up. Stent thrombosis was related to balloon size of less than 3.0 mm, 'bailout' situations, and presence of unstable angina or MI, while bleeding complications were related to being female, duration of postoperative heparin treatment, sheath size, 'bailout' situations, and SVG stenting. However, a high proportion of this group of patients (about 40%) suffered from unstable angina.

The other study (Altmann, *et al.,* 1996) followed 2242 patients at a single referral centre in the USA and compared results of angioplasty before and after stents came into use. Patients treated after introduction of stents tended to have more severe disease at baseline and were more likely to have complications (before stenting), such as diabetes and unstable angina. Despite this, the overall major angioplasty complication rate at the referral centre fell by half, primarily due to a reduction in the need for emergency bypass operations. However, the number of patients actually receiving stents in the study was very small (n = 27) which severely limits the generalisability of these results.

It should be noted that the pace of progress in this area is fast and, as yet, only a few trials of stenting have reached the literature. Results have, however, been presented at conferences and are expected to be published shortly (e.g. the BENESTENT II and STARS studies, and many others). Meta-analyses of the results of these and other trials currently in progress will obviously give a much clearer picture of the importance of coronary stenting.

Medical adjuncts to stenting have also been examined, and two trials of antiplatelet regimens have been carried out. Ticlopidine plus aspirin therapy has been compared with aspirin alone following successful stenting (guided by ultrasound imaging), with no evidence of differences in outcome between the two regimens (Hall, *et al.,* 1996). However, as the authors themselves point out, the sample size is small and the incidence of thrombosis events is low. The study may, therefore, have lacked the power to detect such a difference. Antiplatelet therapy has, however, been shown to result in a lower risk of MI with reduced need for repeated interventions, and less occlusion of the stented vessel, with lower risk of haemorrhagic complications in comparison with anticoagulant therapy in a good-quality RCT of 257 patients (Schomig, *et al.,* 1996). Some of the adverse outcomes in the early stent trials such as BENESTENT are believed to have been caused by the extensive use of anticoagulants such as warfarin. Use of antiplatelet agents rather than anticoagulants significantly reduces of incidence of vascular complications.

Laser angioplasty

One trial has been identified in which laser angioplasty has been evaluated in comparison with standard angioplasty (Appelman, *et al.,* 1996); details are given in appendix 11. The laser technique demonstrated no additional benefit over standard angioplasty and, indeed, had higher longer-term rates of MI and repeat CABG. This is a good quality trial with a description of randomisation, relatively complete follow-up, intention-to-treat analysis and blinded assessment of outcomes.

Directional atherectomy

A third adjunctive procedure for angioplasty is directional atherectomy in which a cutting blade is used in an attempt to remove atherosclerotic tissue and hence improve restenosis rates. Four trials have been identified that compare directional atherectomy with standard angioplasty and these are summarised in appendix 11 (Topol, *et al.,* 1993b (Coronary Angioplasty Versus Excisional

Atherectomy Trial – CAVEAT I); Adelman, *et al.,* 1993; Holmes, *et al.,* 1995). About a third of the patients in the study by Holmes and colleagues had diabetes and the majority of patients in the first two studies (Topol, *et al.,* 1993b; Adelman, *et al.,* 1993) had single-vessel disease. Atherectomy appears to be associated with higher rates of short- and long-term MI and mortality which are not off-set by improved outcomes on other dimensions. Thus, the trials do not demonstrate to date any incremental benefit from atherectomy. These trials are all of good quality, with descriptions of randomisation, complete follow-up, intention-to-treat analyses or clear assessment of withdrawals, and blinded assessment of outcomes.

More recently, a direct comparison of excimer laser, rotational atherectomy and balloon angioplasty (the ERBAC study) has also been reported (Reifart, *et al.,* 1997). This also found that initially superior procedural success with atherectomy was not translated into better long-term (6-month) outcomes.

Longer-term (18 month) follow-up from the Canadian Coronary Atherectomy Trial also found no differences in clinical outcomes between balloon angioplasty and atherectomy (Cohen, *et al.,* 1995). Catheter-based radiotherapy has also been reported to reduce restenosis at 6 months following stent implantation, although the study may be too small to detect differences in clinical outcomes (Teirstein, *et al.,* 1997; for details, see appendix 11).

No observational studies satisfying the review's inclusion criteria have been located in the literature.

Health-related quality of life

No studies of non-medical adjuncts to PTCA were found that fulfilled the inclusion criteria for this review.

Cost and cost-effectiveness

Six cost or cost-effectiveness studies have been identified relating to non-medical adjuncts to PTCA, and these are summarised in appendix 11.

Only one study has been identified which looks at the cost-effectiveness of stenting. Using decision-analytical modelling, the cost-effectiveness of the Palmaz-Schatz stent in patients with symptomatic single-vessel disease was evaluated (Cohen, *et al.,* 1994; Cohen & Baim, 1995) (see appendix 11). The study estimated the expected lifetime hospital costs and lifetime patient benefit (in terms of QALYs) of three treatment strategies:

(a) conventional balloon angioplasty
(b) primary Palmaz-Schatz stenting where stenting is undertaken as part of the initial angioplasty procedure
(c) secondary Palmaz-Schatz stenting where the stent is only used in patients with symptomatic restenosis following initial conventional PTCA.

For a hypothetical 55-year-old male patient, stenting was found to be both more costly and more effective with conventional PTCA, with an base-case incremental cost per additional QALY of US$23,600 (1991 prices). Using a wide range of plausible assumptions, the study found secondary stenting to be both less effective and less cost-effective than primary stenting. On the basis of a detailed sensitivity analysis, the study found that the incremental cost per QALY for primary stenting was less than $40,000 under most plausible assumptions. However, the model could only incorporate clinical data published up to September 1993, many of these being taken from observational studies. Since the model was published, new primary studies have appeared which may make the model's results outdated; the results of the review by Savoie and Sheps (1996) also cast doubt on the effectiveness aspects of this study.

Cohen and colleagues (1995) undertook a comparative hospital cost analysis of conventional angioplasty and Palmaz-Schatz stenting alongside the STRESS trial discussed above (see appendix 11). The analysis was based on detailed resource use data collection from 207 randomised consecutive patients with symptomatic coronary disease requiring revascularisation of a single coronary lesion. Initial mean hospital costs were higher in the stent group (1994 prices): US$9738 (standard deviation (SD), $3428) versus $7505 (SD, $5015). Within the first year of follow-up fewer patients in the stent group required repeat revascularisation, so the higher initial costs of stenting were off-set somewhat. The mean cumulative cost of stenting at 1 year was $11,656 (SD, $5674) compared with $10,865 (SD, $9073) in the PTCA group ($p < 0.001$). Further follow-up will enable a clearer picture to emerge about the relative costs of stents and conventional PTCA.

In a non-randomised comparison of angioplasty and coronary stents in the USA, Dick and

colleagues (1991) found that stents cost 103% more than standard PTCA for a number of reasons, including increased length of stay in hospital, laboratory fees and device costs. The use of fees rather than costs, the small number of patients with stents who were included (27), the possible lack of comparability of the groups, and the fact the study was undertaken in the USA, limit its usefulness to the NHS. Also, stenting practice has changed significantly since 1989–90 when the data were collected.

Three studies compared the cost of angioplasty and atherectomy (Dick, *et al.*, 1991; Topol, *et al.*, 1993b; Guzman, *et al.*, 1994). All of these studies were undertaken in the USA, limiting the value of their information to the NHS. Probably the best of these was the study by Topol and colleagues which was undertaken alongside an RCT. Hospital costs over a period of 6 months were estimated for 297 patients undergoing PTCA and 308 undergoing atherectomy. Total costs were found to be higher for atherectomy (mean total cost of $11,904 versus $10,637 for PTCA ($p = 0.006$)). Dick and colleagues and Guzman and colleagues also found that atherectomy cost more than standard PTCA. Dick and colleagues compared the cost of PTCA, stents and atherectomy and found stents to be the most costly (mean cost: PTCA, $6220; atherectomy, $8329; stent, $12,574). No studies have been located on the cost-effectiveness of atherectomy, although the implication is that atherectomy is dominated by PTCA (i.e. it is more costly and no more effective).

In addition to the six studies looking at the cost or cost-effectiveness of non-medical adjuncts *per se*, Goods and colleagues (1996) looked at cost implications of using warfarin after stenting. Focusing on hospital costs, this non-randomised study in the USA compared 33 patients given warfarin with 33 patients given aspirin and ticlodipine only. The costs of the stenting procedures were similar for both groups. However, the use of warfarin increased length of hospital stay (mean 5.9 days versus 2.1 days; $p < 0.0001$), thus increasing total costs by 33%.

Conclusions

Some evidence exists on stents, atherectomy and laser angioplasty. Although stenting appears to reduce the need for subsequent revascularisation (compared with angioplasty alone) within the first 6 months, methodological problems in the published trials have been identified, and long-term follow-up data is lacking. The evidence regarding the effectiveness of stents is very limited at present and there are few published studies that support the current practice of cardiologists, in whose opinion stents are effective. The results of trials of types of stents other than the Palmaz-Schatz stent are in progress and the publication of these trials may help resolve the uncertainty in this area. The trials looking at medical adjuncts to stenting have shown that aspirin and ticlopidine therapy results in a much lower risk of MI and need for repeated interventions, and less occlusion of the stented vessel, with lower risk of haemorrhagic complications in comparison with anticoagulant therapy.

No evidence exists to indicate the laser angioplasty or atherectomy add any benefit to conventional PTCA.

All the studies of cost and cost-effectiveness of non-medical adjuncts to angioplasty have been undertaken in the USA. All show that adjunctive technologies cost more than angioplasty. Their cost-effectiveness in relation to current UK practice is unknown.

Chapter 10

Medical adjuncts to PTCA

Introduction

In recent years a number of medical therapies have been developed in an attempt to improve the effectiveness of angioplasty. These are reviewed in this chapter.

Clinical effectiveness

Although a number of pharmaceutical adjuncts to angioplasty were in the process of being evaluated in the late 1980s, the RAND and SBU reviews did not report substantive results of any evaluations of these technologies. A range of drug therapies has now been evaluated as adjuncts to PTCA in stable angina, with the objective of reducing MI and restenosis rates. These pharmaceuticals include angiotensin converting enzyme (ACE) inhibitors, anti-thrombotics and corticosteroids. Almost 20 studies have been identified in the literature and a summary of them is presented in appendix 12.

Most of the studies are methodologically of good quality, with relatively complete follow-up, clear description and assessment of withdrawals (often with explicit mention of intention-to-treat analyses), usually with blinded assessment of outcomes and often providing evidence that randomisation resulted in comparable treatment and control groups. Most were conducted outside the UK. Few of these trials detected any important benefits from the addition of drugs to PTCA; however, many of them included only small numbers of patients. The exceptions are discussed below.

Savage and colleagues (1995), found a benefit from the use of aspirin in terms of reduced long-term MI and restenosis rates, in a good quality RCT with descriptions of method of randomisation and withdrawals, and blinded assessment of outcomes. Hoberg and colleagues (1994) found that the use of the calcium channel blocker, verapamil, reduced restenosis rates in patients at high risk of restenosis. The trial is of good quality but there appears to be some lack of comparability in the baseline characteristics of the groups.

One good quality UK study randomised 155 patients to receive epoprostenol or placebo for 36 hours postoperatively in the prevention of restenosis after angioplasty (Gerschlick, 1994). No difference was found at 6-month follow-up using quantitative angiography.

The investigators in the Evaluation of 7E3 for Prevention of Ischemic Complications (EPIC) trial (1994) randomised patients with acute MI or unstable angina or at proven high risk from PTCA to placebo and a new glycoprotein IIb/IIIa receptor in the form of a bolus or bolus plus infusion (see appendix 12). Patients randomised to the active drug benefited from a lower rate of in-hospital MI, CABG and repeat angioplasty. However, the benefits came at the cost of an increased bleeding rate. This may have been a function of the relatively high level of heparin administration: an initial bolus of 10,000–12,000 units was followed by doses of up to 3000 units at 15-minute intervals, and heparin was infused for at least 12 hours postoperatively. A 3-year follow-up from one study of abciximab reported reductions in the need for re-intervention and MI at 1 year without increased bleeding in angioplasty patients at high risk of complications, although no overall reduction in mortality was found (Topol, *et al.*, 1997). No studies that examined the effects of low molecular weight heparin, which would be expected to be associated with a lower risk of bleeding, were identified which met the review's inclusion criteria.

The Studio Trapidil versus Aspirin nella Restenosi Coronarica (STARC) trial compared the platelet-derived growth factor antagonist trapidil with aspirin and found trapidil to be more effective in reducing restenosis after angioplasty, whether restenosis was defined as loss of initial gain of 50%, (24% versus 40%, $p < 0.01$) or as a final stenosis of 50% (31% versus 45%) (Maresta, *et al.*, 1994). At 6-month follow-up, angina was also lower in the trapidil-treated group (26% versus 44%, $p < 0.01$). There were no differences in other cardiovascular events. Further evaluation of trapidil in a larger trial is indicated. This double-blinded trial involved blinded assessment of outcomes and intention-to-treat analysis. In a double-blind RCT, aimed at reducing restenosis rates and the need for repeat

angioplasty in patients with single- or two-vessel disease, an antioxidant probucol has also been compared with placebo at 6 months (Tardiff, *et al.,* 1997).

In addition to these trials, three good-quality meta-analyses have been published in this area, examining the effectiveness of antiplatelet agents, calcium channel blockers and fish oils, respectively.

The Antiplatelet Trialists' reviews provide some indication of the effectiveness of antiplatelet agents in post-PTCA patients (Antiplatelet Trialists' Collaboration, 1994a; b). Pooling of data from four trials (a total of approximately 1300 patients) showed a significant benefit of treatment over placebo; patients receiving antiplatelet therapy showed a reduction of approximately 50% in the odds of MI, stroke or death. Information from 46 trials of antiplatelet therapy on vascular occlusion also indicated a reduction in odds of vascular occlusion of about 44% ($2p < 0.00001$). Treatment for only 6 months still had a significant preventive effect. It was concluded that the benefits of the therapy outweighed the risks of bleeding. As indicated previously, this is a methodologically rigorous review.

The usefulness of calcium antagonists in reducing restenosis after coronary angioplasty has also been demonstrated (Hillegass, *et al.,* 1994). The review was based on a thorough literature search and the included studies were appropriately combined, along with quality assessment of the literature and a sensitivity analysis. It demonstrated the odds of restenosis associated with treatment to be 0.68 (95% CI, 0.49–0.94). The authors suggested that this benefit was clinically meaningful. However, they also recommended that a large RCT should be undertaken to confirm this benefit before the widespread adoption of calcium antagonist therapy, because this finding is based on only five trials with a total of about 900 patients.

Another methodologically robust meta-analysis, involving a thorough literature search and quality assessment of the seven included RCTs, examined the effectiveness of fish oils at doses of 3.5–6.6 g/day in preventing restenosis following angioplasty (Gapinski, *et al.,* 1994). The absolute difference in restenosis rates between treatment and control groups was 13.9% (95%CI, 3.3–24.5%), suggesting a number-needed-to-treat of about 7. A positive linear relationship was found between dosage of omega-3 fatty acids used and the absolute group differences in angiographically-defined restenosis rates ($p < 0.03$). The authors concluded that restenosis is reduced by supplemental fish oils, with the effect being dose-dependent. However, the total number of patients involved was relatively low (< 900) and it has been suggested that further evaluation over a broader range of patients (e.g. older patients with more co-morbidities) is probably required; the side-effects associated with such a dosage have also been emphasised (Cairns, *et al.,* 1996).

Health-related quality of life

No studies of medical adjuncts to angioplasty were found that fulfilled the inclusion criteria.

Cost and cost-effectiveness

One study has been identified in which the relative cost of a medical adjunct to angioplasty is explored (Mark, *et al.,* 1996). This study was undertaken alongside the EPIC trial (see page 47) in which an antiplatelet IIb/IIIa receptor antibody (c7E3 Fab abciximab) was evaluated. The economic sub-study covered 97% of patients (n = 2083) in the trial and included the costs of initial hospitalisation and 6-month follow-up (see appendix 12). Based in the USA, the study took a hospital perspective and expressed its cost results in US$. The reduced rate of ischaemic events in patients taking the active medication reduced initial hospital costs in this group by a mean of $622 but increased bleeding rates off-set the potential saving by a mean of $521 per patient. During the 6-month follow-up, the active drug reduced repeat hospitalisations by 22% ($p = 0.04$), which generated a mean cost saving of $1270 per patient (excluding the cost of abciximab). At 6 months, the total cumulative mean cost per patient of care in the active drug arm was $18,269 compared with $17,976 in the placebo arm ($p = 0.72$), a difference of $293 per patient. The cost-effectiveness of the drug would depend on whether any net additional benefits are generated to justify this additional cost.

No studies assessing the cost-effectiveness of medical adjuncts to PTCA were identified.

Conclusions

Few of the smaller trials detected any important benefits from the addition of drugs to angioplasty,

perhaps because of lack of statistical power.[1] However, there is good evidence, on the basis of the larger trials and a good-quality meta-analysis, that aspirin significantly reduces rates of MI, stroke and vascular death following PTCA, and can reduce the risk of vascular occlusion. The calcium channel antagonist verapamil may also be effective in reducing restenosis rates in patients at high risk of this event, although larger trials are required to confirm this finding. Fish oils may potentially also be very effective in reducing restenosis, although further evaluation is again indicated. The EPIC trial has shown that patients, including those at proven high risk from PTCA, benefited, compared with placebo, from a lower rate of in-hospital MI, CABG and repeat PTCA after taking a new glycoprotein IIb/IIIa receptor monoclonal antibody. However, these benefits came at the cost of an increased bleeding rate. It should be emphasised that the patients in this trial were not typical of those undergoing PTCA, with a large proportion of them being post-MI or having unstable angina.

A cost analysis alongside the EPIC trial showed that, at 6 months, the total cumulative mean cost per patient of care in the active drug arm was $18,269 compared with $17,976 in the placebo arm ($p = 0.72$), a difference of $293 per patient. The cost-effectiveness of the drug would depend on whether any net additional benefits are generated to justify this additional cost. The STARC trial compared the platelet-derived growth factor antagonist trapidil to aspirin and found trapidil to be more effective in reducing restenosis after PTCA, although this finding is based on the results of only one trial and further evaluation is required in a large, long-term study. As trapidil and aspirin need not necessarily be viewed as alternative treatments, such a trial may usefully employ a factorial design to assess the effectiveness and cost-effectiveness of combinations of drugs on morbidity and mortality after PTCA.

Good quality meta-analyses have shown the effectiveness of antiplatelet agents in post-PTCA patients in terms of reducted risk of MI and stroke, and of calcium channel blockers in reducing restenosis after PTCA. A meta-analysis has also shown that restenosis is reduced by supplemental fish oils, although the total number of patients involved is relatively low (< 900) and further evaluation with a broader range of patients is required.

[1] Two RCTs relating to medical adjuncts to PTCA have been published since the formal bibliographic search was undertaken. The EPILOG Investigators (1997) compared abciximab plus standard dose weight-adjusted heparin with abciximab plus low dose weight-adjusted heparin and placebo in 2792 patients, approximately 30% of whom had stable ischaemia. The study found that abciximab plus low dose weight-adjusted heparin markedly reduced the risk of ischaemic complications at no increased risk of bleeding. The IMPACT-II Investigators (1997) assessed another drug to achieve platelet glycoprotein IIb/IIIa receptor blockade, eptifibatide, at two alternative doses compared with placebo in 4010 patients, approximately 60% of whom were low risk. Although both groups with active regimens had lower frequencies of each component of the composite effectiveness measure compared with placebo, the differences in composite effectiveness did not reach statistical significance.

Chapter 11

Overall summary of main findings

Medical treatments

The systematic review of effectiveness of treatments for angina largely confirmed what was already known about the effectiveness of treatments for stable angina. While medical treatments have been shown to be effective in the short-term, there have been few studies of long-term effectiveness, and little evidence that large differences in effectiveness exist between different classes of drug. Beta-blockers have been compared with calcium channel antagonists in four trials of reasonable quality. Studies examining the beta-blockers with vasodilating action and intrinsic sympathomimetic activity showed no evidence that they were more effective than ordinary beta-blockers. However, many of the comparative studies have been small and limited to short-term outcomes, and there have been few studies of both short- and long-term outcomes of combination therapies.

The identified study looking at health-related quality of life showed the negative impact of adverse events on this outcome. A study looking at patients preferences alongside a crossover trial showed that a higher proportion of patients preferred a beta-blocker to a calcium channel blocker (but 36% had no preference). No UK cost or cost-effectiveness studies were identified. The only economic analysis identified looked at the relative cost of three forms of nitrate therapy and, in isolation, provides little policy-relevant information.

CABG versus medical therapy

It appears clear from previous meta-analyses and systematic reviews, and from the majority of recently published RCTs, that CABG has long-term mortality benefits over medical therapy, particularly in patients with greater extent of disease. This difference is evident for up to 5 years and possibly also for longer periods of follow-up (up to 10 years).

No studies formally assessing health-related quality of life with a standardised instrument have been identified in the literature. One study was found showing that initial benefits to patients from CABG, in terms of extent of angina and activity limitation, had disappeared by 10 years.

The economic data relating to the comparison of CABG and medical therapy are limited in the extent to which they reflect contemporary clinical and economic factors in the UK health service. The two full economic evaluations were, when published, considered to be of high quality. Their results reflect the results of effectiveness studies: the greater incremental benefit is generated by CABG in patients with severe angina, left main disease and multi-vessel disease, which is reflected in lower incremental cost per additional quality-adjusted life year ratios for CABG in relation to these subgroups.

PTCA versus medical therapy

The clinical studies comparing angioplasty and medical therapy show some evidence supporting PTCA in terms of relief of angina but the evidence on MI rates is conflicting. This clinical benefit is also apparently reflected in improved health-related quality of life, although information on long-term effects of revascularisation is lacking. In one Australian cost-effectiveness analysis, angioplasty was considered cost-effective on the basis of an incremental cost of A$3875 per extra patient free of angina.

PTCA versus CABG

The relative effectiveness of CABG and angioplasty has been most clearly illustrated in several recent good quality meta-analyses. These have shown that CABG is less likely to result in further therapeutic interventions than PTCA and also to result in a lower incidence of angina at 1-year follow-up. However, the difference between in angina rates is likely to have declined by 3 years. No differences have emerged between PTCA and CABG in terms of mortality and non-fatal MI.

The results of a large observational study found that patients with single-vessel disease (apart from those with at least 95% proximal LAD stenosis) showed greater benefit from angioplasty than CABG. Patients with three-vessel disease, and those with two-vessel disease and at least 95% proximal LAD stenosis, benefited more from CABG than

PTCA. Survival benefit was similar for either revascularisation procedure in all other patients with two-vessel disease, and patients with single-vessel disease with at least 95% proximal LAD stenosis. Absolute survival benefit was found to be greatest in patients with severe three-vessel disease treated with CABG compared with similar patients undergoing PTCA.

Studies comparing CABG and PTCA in terms of health-related quality of life have not shown differences but this may be due largely to methodological problems in the studies. Indirect assessment of quality of life (via reductions in rates of angina) shows a benefit for CABG over PTCA.

The relative cost of the two procedures depends on the point of follow-up. The most recent UK cost analysis showed an initial mean cost of angioplasty which was 52% that of the cost of CABG, a proportion that increased to 81% at 2 years. However, the results of a modelling study in the USA published in 1990, and of reasonable quality, indicated that angioplasty is likely to be more cost-effective than CABG as long as complete revascularisation is possible, which may not be feasible in patients with three-vessel disease. However, this trial was undertaken prior to the availability of trial data and its results should be treated with caution. No recent cost-effectiveness analyses have been identified, and none at all relating to UK practice. The most recent, undertaken in the USA using non-trial data and requiring caution in interpretation, concluded that angioplasty is likely to be more cost-effective than CABG as long as complete revascularisation is possible, which may not be feasible in patients with three-vessel disease.

Non-comparative studies of CABG

CABG relieves angina in the large majority of patients undergoing surgery, and it further appears that IMA grafts are associated with greater long-term patency and less angina at long-term follow-up than non-IMA grafts. The results of large observational studies also suggest that CABG relieves angina in the majority of patients, with about 1% of patients needing reoperation each subsequent year. Many outcomes of surgery appear to be slightly worse for women than men, and for older patients; for example, relief of angina and long-term mortality are both age-related. Short- and longer-term mortality also show a clear association with disease severity (number of vessels diseased), ejection fraction and initial severity of angina.

Along with improvements in functional status, CABG also brings improvements in health-related quality of life; physical, sexual and social functioning improve significantly in the large majority of patients. No published economic analyses were found that are likely to be helpful to decision makers in the NHS.

Medical adjuncts to CABG

There is clear evidence that aspirin reduces the odds of occlusion after CABG; thus, aspirin can be considered effective in this context. It need not necessarily be viewed as an alternative to other medical treatments, as it may also be possible for it to be used in addition to other treatments (unless contraindicated). Of the studies which were identified, most examined aspirin (with or without dipyridamole) or warfarin – which is no longer routinely used in this context. There appears to be little difference in effectiveness between aspirin and warfarin, although warfarin may result in greater bleeding. No health-related quality of life or economic studies were found in the literature.

Non-comparative studies of PTCA

Non-comparative studies of angioplasty have found that results, in terms of survival, angina, MI and rates of re-intervention, are better in patients with single-vessel rather than multi-vessel disease. Success of PTCA is also influenced by age of patient and angina class. Although left ventricular disease is associated with poor outcomes, PTCA can still be effective in these patients. Health-related quality of life has been shown to improve after PTCA but no information is available on key subgroups in this regard. No evidence was identified on cost or cost-effectiveness.

Non-medical adjuncts to PTCA

Some evidence exists on stents, atherectomy and laser angioplasty. Although stenting appears to reduce the need for subsequent revascularisation within the first 6 months (compared with angioplasty alone), methodological problems in the published trials have been identified and long-term follow-up data is lacking. The evidence regarding the effectiveness of stents is very limited at present. Not only are there few published studies but the literature may lag behind current practice in cardiology, where they are considered by surgeons

to be effective. The results of trials of types other than the Palmaz-Schatz stent are in progress and the publication of these trials may help resolve the uncertainty in this area.

The trials looking at medical adjuncts to stenting show that aspirin therapy results in a lower risk of MI, with the need for repeated interventions, and less occlusion of the stented vessel, with lower risk of haemorrhagic complications in comparison with anticoagulant therapy.

A small number of studies of other non-medical adjuncts of angioplasty were identified; these indicate no benefit from directional atherectomy or laser angioplasty in trials of over 300 patients.

There is, as yet, no information on the relative cost-effectiveness of non-medical adjuncts to angioplasty.

Medical adjuncts to PTCA

Few of the included trials detected any important benefits from the addition of drugs to angioplasty but many of them covered small numbers of patients. On the basis of the larger trials, evidence exists of benefit from the use of aspirin, in terms of reduced long-term MI and restenosis rates. Moreover, aspirin need not be viewed as an alternative to other drugs and, unless contraindicated, can be considered as an additional treatment. The usefulness of calcium antagonists in reducing restenosis after coronary angioplasty has also been demonstrated in a systematic review. However, this finding is based on only five trials with a total of about 900 patients.

The EPIC trial has shown that, compared with placebo, patients, including those at proven high risk from angioplasty, benefited from a lower rate of in-hospital MI, CABG and repeat angioplasty after taking a new glycoprotein IIb/IIIa receptor monoclonal antibody. However, these benefits came at the cost of an increased bleeding rate. It should be emphasised that the patients in this trial were not typical of those undergoing angioplasty, a large proportion being post-MI or having unstable angina. Trials published very recently will help to reduce uncertainty in this area.

A cost analysis alongside the EPIC trial showed that, at 6 months, the total cumulative mean cost per patient of care in the active drug arm was US$18,269 compared to $17,976 in the placebo arm ($p = 0.72$), a difference of $293 per patient. The cost-effectiveness of the drug would depend on whether any net additional benefits are generated to justify this additional cost. The STARC trial compared the platelet-derived growth factor antagonist trapidil with aspirin and found trapidil to be more effective in reducing restenosis after angioplasty; however, longer-term assessment in a larger trial is required to determine its effectiveness and cost-effectiveness both in comparison, and when used in addition, to aspirin.

Good quality meta-analyses have shown the effectiveness of antiplatelet agents in post-PTCA patients in terms of reducted risk of MI and stroke. A meta-analysis has also shown that restenosis is reduced by supplemental fish oils, although the total number of patients involved is relatively low (< 900) and further evaluation over a broader range of patients is required.

Conclusions

A wide range of studies evaluating the impact of alternative interventions on stable angina has been considered in this review in terms of clinical outcomes, health-related quality of life and cost and cost-effectiveness. In the next chapter we attempt to place the results of the review in a decision-making context.

Chapter 12

Placing the systematic review into context

Introduction

The aims of this chapter are as follows:

- to summarise the main findings of the systematic review in terms of effectiveness and cost-effectiveness
- to note the necessary limitations of the review and to stress the importance of other related issues not covered by this review
- to suggest a means of translating this systematic review evidence into clinical or commissioning policy, recognising that, in the short- and medium-term, decisions will have to be made even when good evidence is lacking
- to propose a number of priorities for future research and development relating to the management of stable angina, which would help to fill the more important gaps in evidence.

A summary of effectiveness and cost-effectiveness of alternative treatments for stable angina

In chapters 3–10 summaries were provided at the end of each comparison and these were drawn together in chapter 11. In *Table 5,* to be consistent, an overall summary is presented of the key evidence generated by the systematic literature review in relation to comparisons of the main interventions covered. For each comparison, a summary of evidence relating to effectiveness (clinical and health-related quality of life) and cost-effectiveness is presented, in each case both in general terms and in relation to key subgroups of patients.

Discussion of these summary conclusions with our Expert Panel emphasised that, in some areas, firm clinical opinion exists which this review has found neither evidence to support nor to refute. For example, in the medical management of stable angina, some members of the panel suggested that two anti-anginal drugs are more effective in relieving angina symptoms than one but that the addition of a third adds little benefit. 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). This opinion may reflect evidence excluded from this review because, for example, of the numbers of patients or the design of the studies.

Despite the available number of studies in this area, the overall picture that emerges is not clear. A number of choices are highlighted in *Table 5* in which the evidence is reasonably clear but many of these are drawn from studies of highly selected patients. This serves to emphasise that we 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.

The limitations of the review

Two types of limitation need to be recognised. The first is methodological and reflects the inherent problems in undertaking a systematic review of a broad area such as this, on a topic which is the subject of an ever-growing body of literature. The review has used clear and explicit search strategies and inclusion criteria for studies (and these are fully explained). Some have necessarily been chosen to make an enormous undertaking feasible. While these strategies and criteria can be well-defended, they cannot guarantee that all valuable evidence has been included. More significantly, new material is being published all the time and this review will be out of date almost as soon as it is published. This highlights the importance of the Cochrane Collaboration review groups, which seek to maintain and regularly update systematic reviews of healthcare interventions. Users need to be vigilant in identifying more recent publications and in assessing whether these would change the balance of evidence on any issue. For example, no studies on transmyocardial revascularisation or minimally invasive bypass grafting have fulfilled the inclusion criteria of this review, although studies are under way or planned.

TABLE 5 *Summary of evidence from the systematic review*

Intervention	Effectiveness	Cost and cost-effectiveness
Medical	***(i) Systematic review: in general*** Direct comparisons show no evidence of important differences in long-term (≥ 6 months) effectiveness and safety between different medical therapies. This applies across range of outcomes including exercise duration. Similarly, combinations of beta-blockers and calcium channel blockers show no long-term benefit over either drug alone. No clear evidence of difference between beta-blockers and nitrates in long-term effectiveness. Generally, however, trials were low-powered with little information on adverse effects. There is also good evidence that antiplatelet treatment is effective in preventing MI, stroke and death in patients at high risk, and MI in patients at low risk. ***(ii) Systematic review: key subgroups*** No evidence was found to suggest major sub-group differences in long-term effectiveness of medical therapies.	***(i) Systematic review: in general*** No information on differences in cost or cost-effectiveness between different classes of medical therapies, except one modelling study that suggested that isosorbide mononitrate is more cost-effective than other nitrates. ***(ii) Systematic review: key subgroups*** No information on differences in cost or cost-effectiveness between different subgroups.
PTCA vs. medical	***(i) Systematic review: in general*** Long-term good quality studies suggest that PTCA is more effective in relieving symptoms than medical therapy in patients with more severe angina at baseline. Moreover, relief is likely to be more complete and achieved sooner with PTCA. At 3-year follow-up both mortality and MI rates likely to be similar with PTCA and medical treatment, although larger studies are needed to confirm this. However, PTCA patients likely to experience greater improvements in HRQoL compared with those receiving medical therapy, although information on long-term effects of revascularisation is lacking. ***(ii) Systematic review: key patient subgroups*** Little information found on relative effectiveness in different subgroups of patients. Greater long-term effectiveness for PTCA mainly observed in patients with single-vessel disease.	***(i) Systematic review: in general*** No information on differences in cost or cost-effectiveness (see below for single-vessel disease). ***(ii) Systematic review: key patient subgroups*** No information on differences in cost or cost-effectiveness other than one Australian modelling study which suggested that medical therapy more cost-effective for hospital than PTCA in single-vessel disease.
CABG vs. medical	***(i) Systematic review: in general*** Clear that CABG associated with lower long-term mortality than medical therapy. This difference has been shown at 5-, 7- and 10-year follow-up. Risk reduction is greatest in those at moderate to high risk. No studies formally assessing HRQoL with standardised instrument identified in the literature. This difference is related to greater angina relief, greater improvement in physical functioning and less need for anginal medications in those undergoing CABG. ***(ii) Systematic review: key patient subgroups*** Several patient subgroups have been shown to benefit from CABG compared with medical therapy. 5-year mortality significantly reduced for patients with left main artery disease or 3-vessel disease. Among those receiving CABG, mortality reduced in CABG patients with proximal LAD stenosis in multi-vessel disease; among those without LAD stenosis, mortality significantly reduced only in those with 3-vessel disease or left main artery disease. LVF is also determinant of survival benefit. Overall, benefit of treatment with CABG appears to be greater in patients at higher risk.	***(i) Systematic review: in general*** Economic data relating to comparison of CABG and medical therapy limited in extent to which they reflect contemporary clinical and economic factors in UK health service. Relative cost-effectiveness depends crucially on patient sub-group (see below). ***(ii) Systematic review: key patient subgroups*** Study results reflect results of effectiveness studies: greater incremental benefit generated by CABG in patients with severe angina, left main disease and multi-vessel disease, and reflected in lower incremental cost per additional QALY ratios for CABG in relation to these subgroups.
PTCA vs. CABG	***(i) Systematic review: in general*** RCTs based on highly selected group of patients. No apparent difference in long-term mortality rates between PTCA and CABG. There appears to be no difference in short-term MI rates. However, CABG more effective than PTCA in relief of angina, at least up to 3-year follow-up, and patients undergoing CABG less likely to need re-intervention. This difference in re-intervention rates most pronounced in first postoperative years and difference attenuates thereafter. There is some indirect evidence of greater improvement in HRQoL with CABG than with PTCA, based on greater reduction in angina incidence in CABG patients. ***(ii) Systematic review: key patient subgroups*** Differences between PTCA and CABG in need for re-intervention and angina rates found both in patients with multi-vessel and single-vessel disease. A large observational study found that patients with 1-vessel disease (apart from those with at least 95% proximal LAD stenosis) showed greater benefit with PTCA than CABG. Patients with 3-vessel disease, and those with 2-vessel disease and at least 95% proximal LAD stenosis, benefited more from CABG than PTCA. Survival benefit similar for either revascularisation procedure in all other patients with 2-vessel disease, and patients with at least 95% proximal LAD stenosis only. Absolute survival benefit found to be greatest in patients with severe 3-vessel disease treated with CABG compared with similar patients undergoing PTCA.	***(i) Systematic review: in general*** Several cost analyses run beside RCTs. Most studies show that initial costs higher for CABG than PTCA. Due to lower re-intervention rates for CABG, difference in cost to health service reduces over time, although based on follow-up to date CABG remains more costly option. ***(ii) Systematic review: key patient subgroups*** Cost analyses suggest that PTCA less costly than CABG in both single- and multi-vessel disease, at least in short-term follow-up. Modelling study (USA) using non-trial data concluded that PTCA likely to be more cost-effective than CABG as long as complete re-vascularisation possible.

continued

TABLE 5 contd *Summary of evidence from the systematic review*

Intervention	Effectiveness	Cost and cost-effectiveness
Standard PTCA vs. stents	***(i) Systematic review: in general*** Trials have suggested that stenting associated with lower short-term incidence of cardiovascular events compared with standard PTCA, and with reduction in risk of repeat revascularisation. However, trials to date have been performed in highly selected population and evidence for use of stents in majority of patients with coronary artery disease is limited. Although few published trials, opinion of cardiologists is that stents very effective. Results of trials of types other than the Palmaz-Schatz stent in progress, and publication of these trials may help resolve the uncertainty in this area. ***(ii) Systematic review: key patient subgroups*** There is too little information available to comment on the relative effectiveness in different subgroups. The patients included in the relevant published trials are mainly aged 75 years or less, and the majority have single-vessel disease.	***(i) Systematic review: in general*** Two studies show that initial costs (hospital and one year) increased by use of stenting. However, much of this attributable to anticoagulation increasing length of hospital stay. One further study suggests that not using warfarin after stenting, just aspirin, could reduce cost of stenting. One economic modelling study suggests that primary stenting more costly but more effective than PTCA, but quality of clinical evidence poor. Also, one study showed bare trans-radial stenting to be much less costly to hospital than sheathed trans-femoral stenting. ***(ii) Systematic review: key patient subgroups*** One economic modelling study suggests primary stenting more costly but more effective than PTCA alone in patients with 1-vessel disease. Least cost-effective option is PTCA followed by stenting if PTCA fails. Again, clinical evidence is crucial to this. Also, in 1-vessel disease, one study showed bare trans-radial stenting to be much less costly to hospital than sheathed trans-femoral stenting.
Standard PTCA vs. atherectomy	***(i) Systematic review: in general*** Trials published to date which compare directional atherectomy with standard angioplasty demonstrate no additional benefit for atherectomy. Although initial results (i.e. initial increase in lumen size) better with atherectomy, this offset by procedure's subsequent higher short- and long-term MI and mortality rates. ***(ii) Systematic review: key patient subgroups*** Atherectomy results apply mainly to patients with single-vessel disease.	***(i) Systematic review: in general*** Three studies show that initial costs increased by use of atherectomy. This accompanied by lower success rate, making atherectomy less cost-effective than PTCA. ***(ii) Systematic review: key patient subgroups*** Two studies show initial costs increased by use of atherectomy in patients with single-vessel disease. This is accompanied by lower success rate, making atherectomy less cost-effective than PTCA in patients with single-vessel disease.
Standard PTCA vs. medical adjuncts	***(i) Systematic review: in general*** Although many trials examined various drug adjuncts to PTCA, few demonstrated any additional significant benefit of these medical treatments. However, antiplatelet agents shown to reduce odds of MI, stroke or death following PTCA by about 50%. Trials very recently published (i.e. in 1997) will help to reduce uncertainty in this area. Some evidence suggests that supplemental fish oils also significantly reduce restenosis rates, although further evaluation of this finding probably required. ***(ii) Systematic review: key patient subgroups*** No clear evidence of differential effectiveness in subgroups available.	***(i) Systematic review: in general*** Little information on differences in costs and cost-effectiveness. Use of abciximab to reduce restenosis rates resulted in no increase in costs to hospital in first 6 months. ***(ii) Systematic review: key patient subgroups*** Little information on differences in costs and cost-effectiveness.
Standard CABG vs. adjuncts	***(i) Systematic review: in general*** Antiplatelet agents (such as aspirin and aspirin plus dipyridamole) appear to be effective in reducing re-occlusion at long-term follow-up. Warfarin (no longer in use) appears effective, although its safety is unclear. ***(ii) Systematic review: key patient subgroups*** The benefit of treatment with aspirin is observed in both patients undergoing SVGs and patients undergoing left IMA grafts. Graft patency is more common in men than in women.	***(i) Systematic review: in general*** No information on differences in costs and cost-effectiveness. ***(ii) Systematic review: key patient subgroups*** No information on differences in costs and cost-effectiveness.

The second limitation is that the question of the most appropriate treatments for stable angina has to be viewed as one question alongside other related questions that this review did not seek to answer. Systematic reviews already undertaken, or to be undertaken in the future, will complement the present study. The Expert Panel noted, in particular, an additional need to consider the evidence on:

- when and how, most appropriately, to investigate the diagnosis of stable angina at the primary care level and to decide when to treat medically or to refer for specialist review
- the role of behavioural interventions aimed at reducing cardiovascular risk factors (including weight, smoking status and exercise levels) in these patients
- the role and value of interventions such as statins to treat the disease process of angina.

The therapeutic choices relating to stable angina that are the subject of this review need to be viewed as but a part of the determination of

an appropriate therapeutic strategy for these patients. This would include advice regarding smoking cessation (which would be expected to improve outcomes after coronary artery bypass surgery and angioplasty) and interventions to lower blood cholesterol in appropriate patients.

It is clear, however, that there is also a widely-perceived need for local, research-based guidance on the indications for referral, further assessment and treatment of stable angina.

Making decisions using evidence

The limitations of evidence from systematic review

The conclusions that can be drawn from the evidence considered in this systematic review do not provide, in isolation, an adequate basis for decision makers to make decisions about resource allocation at local level. In this case, as more generally, a range of information problems still remain.

- Good evidence about certain elements of effectiveness and cost-effectiveness is not available. For example, this systematic review indicates that there is **little** good trial evidence on the effectiveness of stents in PTCA compared with standard PTCA in the range of clinical subgroups associated with stable angina. However, it is important to note the clinicians' view, based on practical experience, that stents are beneficial to patients. It is, therefore, essential that, when the results of on-going trials of stents become available, there is a thorough review of whether their widespread use is justified.
- Additionally a range of locally specific information is needed:
  - local epidemiological data relating to the incidence and prevalence of stable angina, and the size of particular clinical sub-groups of patient
  - information on local cost structures and available patterns of care which may well exhibit considerable variation between centres and differ from those reflected in the cost-effectiveness studies reviewed (the importance of this point is highlighted by the fact that many of the clinical and economic evaluations in this review are from the USA and their relevance to any particular locality in the UK must be tested very cautiously)
  - contextual information on locally-imposed constraints, such as the current relative availability of interventions on, for example, relevant policy initiatives.
- One implication of the evidence, as touched on above, is that any decision about the relative benefit offered by alternative forms of clinical management involves values or preference weightings being placed on the range of outcomes generated by an intervention. Some of the economic evaluations reviewed included the valuation of relative outcomes. However, such data are rare and, even when they have been generated, may be considered unrepresentative of the values of patients or the general public in a specific location. Hence decision makers may need local information on public or patients' values or preference weightings.
- For healthcare commissioners, the evidence may imply that they should not be making a blanket decision to provide only one form of intervention to such patients but that the various main forms of treatment for stable angina should be available, and the route of access such that patients are appropriately informed of the therapeutic options and not simply offered a single therapy based on provider preferences.

A role for decision analysis

Given the multiple factors, in addition to the results of the systematic review, that will need to be taken into account in order to make decisions about resource allocation, local decision makers need a framework within which to handle the various elements of data. Dowie (1996a; b) has proposed that decision analysis has a major role to play. Using the language of decision trees and probabilities, decision analysis provides both a framework for communicating the issues and uncertainty associated with resource allocation decision making, and an explicit and transparent means of reaching decisions (Weinstein, *et al.*, 1980; Sox, *et al.*, 1988; Thornton & Lilford, 1995). In principle, the analytical vehicle of the decision tree enables clinical and epidemiological evidence from systematic reviews to be presented in such a way that local decision makers can augment the tree with local cost data, suitable preference values and explicit judgements about how trial results apply to the specific patients in their area, in order to reach decisions in the local context.

An illustrative example of the use of decision analysis to inform local healthcare decision makers in the management of stable angina is presented in appendix 14 (Dowie R, 1996). The data inputs

into this decision tree have been assembled independently of this review and reflect the evidence perceived as being locally relevant. Hence, it should be taken as an illustration of how this approach might be used locally rather than a definitive case study consistent with the evidence identified in this review. It emphasises that, in order to make policy decisions, assumptions have to be made about likely values of a range of parameters for which, unfortunately, there may be no good evidential basis.

Research needs and priorities

From the results of the review and the advice from the Expert Panel, the major information gaps in the costs and benefits of alternative treatments for stable angina have been identified, together with those areas where further research and development is required. These include:

- adequately-powered and long-term studies of the relative costs and effects of rational combinations of medical treatments
- the cost and cost-effectiveness of PTCA compared with medical therapy
- the evaluation of the effectiveness and cost-effectiveness of new types of stent
- the assessment of the effectiveness and cost-effectiveness of the new generation medical and non-medical adjuncts to PTCA and CABG;[1] fish oils, in particular, have the potential to provide a cost-effective method of preventing restenosis rates after PTCA, although there have been only a few small trials, and further assessment of this adjunctive treatment is warranted
- the assessment of the effectiveness and cost-effectiveness of new interventions such as transmyocardial revascularisation (Horvath, *et al.,* 1997) and minimally invasive bypass grafting (Calafiore, *et al.,* 1996)
- patients' treatment- and health-related preferences regarding stable angina; although some work of this type has been identified in the review process (Nease, *et al.,* 1995; Chestnut, *et al.,* 1996),[2] it needs to be used to inform resource allocation directly by relating it to particular treatment comparisons
- formal evaluation of new technologies before they become widely diffused into clinical practice should be ensured to avoid the situation that has occurred with stenting
- more economic evaluations of alternative treatments for stable angina need to be undertaken; studies need to relate to a wider selection of technologies and to reach a higher methodological standard than the majority of economic studies published in this clinical area to date.

A final general point should be made regarding the conduct of future trials in this area. The main sources of bias in trials of healthcare interventions are now well-known, and the Cochrane Collaboration emphasises four main sources of bias: selection bias (the bias that results from the way that the groups to be compared are assembled), performance bias (systematic differences in care provided to the comparison groups, other than the intervention of interest), attrition bias (systematic differences between groups in loss of participants from the study), and detection bias (systematic differences in outcome assessment). Future trials should make every attempt to control the sources of these biases by:

- adequate concealment of assignment of patients to groups until treatment has been assigned
- using double-blinding where possible, in addition to blinded assessment of outcomes
- full reporting of losses of participants to follow-up.

In addition, other methodological comments relating to RCTs in this area may be appropriate. In particular, the benefits of factorial designs in RCTs may be considered, for example to test the additional benefits derived from using combinations of treatments. This type of trial might be appropriate, for example, where two drugs are believed to act on different platelet mechanisms, and where their effects may expected to be additive. This would also avoid the implication of trials in which medical therapies are compared that such drugs should be viewed solely as alternatives.

Whatever designs are adopted for future RCTs, systematic overviews and meta-analyses of trials will continue to have an important place in the assessment of healthcare interventions. To ensure these reviews are not compromised by publication bias, there is a need for full (and prompt) publication of the results of all trials, irrespective of their findings.

[1] This would involve evaluation of the new minimal access approaches to CABG.

[2] These studies were not included in the review as they do not relate to specific treatments.

In conclusion, it should be emphasised that the treatments reviewed in this section should be viewed as only one component of the management of stable angina. They should, therefore, be considered in the general context of overall lifestyle change and risk factor modification in such patients, including smoking cessation and lipid-lowering interventions.

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The views expressed in the document, together with any errors, are the responsibility of the Review Team alone.

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Appendix 1

The quality criteria used to assess published systematic reviews and meta-analyses

Quality assessment of SBU and RAND literature reviews of CABG and PTCA

Objectives of the SBU and RAND reports

SBU

The objectives of the SBU and RAND reviews were slightly different from those of the current review. The main objectives of the SBU report were to judge the effectiveness of CABG and PTCA according to a specific set of outcomes and risks. Although there is some reference to improvement in symptoms and health-related quality of life, survival is given greater prominence. In the main, the SBU review compares CABG with PTCA and both of these with medical treatment, in order to provide a background to the main body of the report on the appropriateness of these procedures. However, although the focus is mainly on effectiveness, there is some consideration of changes in technology. Greater emphasis is given to PTCA than CABG.

RAND

This review was undertaken in order to summarise the evidence for a panel who were producing appropriateness ratings for a large number of indications. The stated aim was to "review the literature concerning effectiveness and risks of CABG (and PTCA), provide a comprehensive list of potential indications for CABG and PTCA and present ratings of appropriateness". The specific outcomes assessed are similar to those assessed in the SBU review. The focus is again on effectiveness, indications and appropriateness, and the main outcomes of interest are similar to those of the SBU review. Again, there is some information on technology assessment but this is not a main objective of the review.

Specific interventions included/excluded

SBU: CABG and PTCA

Comparisons of CABG with PTCA and of either of these with medical treatment were eligible for inclusion. The PTCA group included, for example, lasers, atherectomy and stents, although no RCTs in these areas are reported.

RAND: CABG review

A brief review of changes in surgical techniques is included but the main focus is on effectiveness of CABG. Comparisons with medical therapy are included.

RAND: PTCA review

Coronary reperfusion catheters and atherectomy are excluded. Intracoronary stents and drugs in prevention of restenosis are not reviewed in detail (see pages 8–9 of the review).

Types of patient included in the reviews

SBU

The review is organised by indications for treatment. One chapter of the literature review specifically relates to patients with chronic stable angina.

RAND

Patients with chronic stable angina are also considered as a separate sub-group in the RAND reviews.

Outcomes assessed

SBU

For CABG, the major clinical outcomes were relief of angina symptoms, prevention of MI and long-term survival. The major risks assessed were postoperative mortality and complications (perioperative MI and stroke). The major clinical outcomes were similar for PTCA, while the major complications included death, MI and need for emergency CABG.

One controlled trial of PTCA was also identified which assessed 'return to work' as an outcome indicating change in health-related quality of life.

RAND

The clinical outcomes for CABG and PTCA were the same as those for the SBU review. As well as mortality, risks of death and major and minor complications are summarised for both procedures.

Study designs included

SBU

RCTs comparing CABG, PTCA and medical treatment were included, together with

observational studies of risks of CABG and PTCA where necessary.

RAND: CABG review

RCTs and prospective cohort and registry studies were given precedence. Observational data were usually not reported, although there were a few exceptions.

RAND: PTCA review

Because PTCA was then a relatively new technique, it was not possible to restrict the studies included to RCTs. This means that the data are mainly from uncontrolled studies. There appear to be no restrictions on the type of study design contributing data on complications of PTCA. However, the commentary highlights potential biases in particular trials when reporting results. 'Very small' series were excluded unless they provided important descriptive information.

Although RCTs which compared CABG with medical therapy were included, no RCTs were found that directly compared CABG and PTCA; hence, data are presented from observational studies. No RCTs were found that compared PTCA with medical treatment.

Methodological quality

Search

The search undertaken for the SBU literature review relied heavily on MEDLINE. The information staff at the NHS Centre for Reviews and Dissemination have suggested that there should be strong reservations about the comprehensiveness of the search, as MEDLINE does not give good coverage of pharmaceutical journals. Some evidence of searching of other databases (e.g. EMBASE) and probably some of the on-line drugs databases would be an advantage. The review found very little in the way of RCTs comparing medical therapy with PTCA or CABG (and no new trials at all that compared CABG with medical therapy). It is possible that a search of other databases would uncover relevant trials in this area.

Another criticism of the search strategy of the SBU review is that, in searching MEDLINE, only MeSH headings were used. This assumes that the headings are correct and that MEDLINE indexing is accurate and consistent. However, some studies may be missed if they are indexed incorrectly. Searching the text of abstracts may have uncovered other studies.

Similar criticism can be made of the RAND reviewers, in that they also confined themselves to MEDLINE searches and examination of the bibliographies of the retrieved articles. No search strategy is presented in the review (i.e. no details are given of the search terms or how they were used).

Inclusion/exclusion criteria

Non-English language studies were excluded from both the SBU review and the two RAND reviews. There is no information in any of the reviews to indicate the number of non-English studies this excluded; hence, it is not possible to say whether or not this is likely to have had a significant effect. This may not have resulted in the exclusion of many trials in the area of chronic stable angina – for example, in the SBU review no trials of medical therapy in English were found on MEDLINE but a subsequent MEDLINE search reveals that there do not seem to be any non-English language trials either. However, excluding non-English studies may have had a greater effect if EMBASE had been searched – EMBASE has much wider coverage of European journals and relevant non-English language articles may have been found there.

No information is presented in either review which indicates how judgements were made on which studies should be included or excluded.

Data extraction

No information is given on the method of data extraction in either the RAND or SBU reviews (e.g. by one reviewer or two independent reviewers), or on how differences between reviewers about inclusion of data were resolved.

Data synthesis

In the SBU review, studies are generally combined narratively rather than by calculating overall summary statistics and are, therefore, simply listed with the main finding presented for each primary study. Included studies appear to be listed in priority order, with RCTs (where available) first followed by observational studies. Results from RCTs and observational studies are not combined using any weighting system, but results from some observational studies are summarised separately using averages weighted by study size.

In the RAND reviews summarisation of data from RCTs is mainly narrative (where available). However, average effects are calculated (i.e. where appropriate data can be pooled). For example, an average operative mortality rate after CABG and a weighted average rate of emergency CABG in PTCA are calculated.

Investigation of heterogeneity

Differences between studies are highlighted in detailed narrative in both the SBU and RAND reviews, although there is no quantitative assessment of heterogeneity. The RAND results are also examined grouped by study design, and it is noted that the results from uncontrolled studies were superior to results from controlled studies which, in turn, were superior to results from RCTs. Results are also analysed in sub-groups where appropriate (e.g. diabetics, obese patients and smokers).

Assessment of validity or quality of primary studies

It is unclear generally from both these reviews just how quality assessment was used. There was some broad quality assessment, insofar as primary studies are ranked with RCTs at the top and observational studies below. For example, in the RAND review, there is some discussion of differences between individual RCTs. However, there appears to be no clear and consistent assessment of the quality of the studies beyond categorising them according to study design.

Although the RAND CABG review identifies many sources of bias, some particularly important in RCTs of CABG, there appears to be no consistent assessment of the quality of individual studies. That is, there are no criteria for differentiation between RCTs of different quality, although individual studies are criticised.

Major conclusions specific to chronic stable angina

SBU – CABG

1. CABG increases survival in patients with severe coronary disease.
2. Complication rates increased between 1981 and 1987 as surgery was extended to old and severely ill patients.
3. There have been no results from new RCTs since RAND.

SBU – PTCA

1. PTCA is more effective than medical treatment in relieving angina and improving exercise test performance.
2. PTCA is controversial in patients with left ventricular dysfunction.
3. PTCA should not be used in protected left main artery stenosis unless CABG is not possible.
4. The long-term benefit of PTCA in total occlusion is controversial.
5. Vein graft PTCA has the same outcome rate as native vessel PTCA.

SBU – CABG versus PTCA

The interim report from one RCT indicates no difference between CABG and PTCA in terms of mortality and non-fatal MI but CABG is more effective in relieving angina. Repeat procedure rate is also lower with CABG.

RAND – CABG

1. CABG is much more effective than medical therapy in relief of angina.
2. Risk of later MI is not reduced, however, except possibly in patients with three-vessel disease.
3. Long-term survival is improved in patients with left main coronary artery disease, three-vessel disease with reduced left ventricular function, and two-vessel disease with proximal left anterior descending involvement.
4. Survival is higher in surgical patients with three- or two-vessel disease with a highly positive exercise ECG.

RAND – PTCA

1. Weighted average primary success rate for PTCA is about 85%.
2. Restenosis rate is about 30% over 18 months.
3. Approximately 20% of patients will require repeat PTCA.
4. Approximately 20% of patients experience recurrent angina within 1–2 years.
5. Rates of subsequent CABG range from 8% to 13% among patients followed for ≥ 6 months.

No reports were found that compared PTCA with CABG.

Additional general areas not covered by these reviews

The following areas which are covered in the current review are not covered by the SBU or RAND reviews.

1. There appears to be little information available from the SBU review to allow the effectiveness of new technologies in PTCA to be examined fully.
2. The SBU update highlighted a relative lack of information on CABG compared with PTCA in chronic stable angina and comparisons of PTCA and medical therapy.
3. Information on health-related quality of life was largely lacking from both reviews. It is unclear whether information on this issue was actively sought, or whether it simply did not appear in the studies which were finally included in the reviews. Information on patient preferences is similarly absent.
4. Cost and cost-effectiveness was not a focus of either the RAND or SBU reviews. Also,

although some information is presented on costs and utilisation, the information is not relevant to the UK.

5. The epidemiological background information in these reviews is rather limited, although it is not clear whether this part of the reviews is intended to be comprehensive or systematic.

Assessment summary

The main body of the SBU report appears to be a reasonable systematic review. For example, it would be included on the NHS CRD Database of Abstracts of Reviews of Effectiveness (DARE). However, the inclusion and exclusion criteria for trials are not clear – either in terms of what they were or how they were applied. For example, priority was given to RCTs but it is not always clear how this prioritisation contributes to the conclusions and recommendations given in the summary.

The search strategies are limited in terms of coverage. The RAND search strategy is not described in enough detail to determine how the search was carried out.

One positive feature of both reviews is that there was some consideration of the differences between studies. Although the investigation of heterogeneity is narrative rather than quantitative, both reviews did consider how differences could affect interpretation in some detail. For example, the SBU review examines the wider applicability of some results to other populations. The RAND reviews tend to present more commentary on the validity (or biases) of individual studies.

Thus the SBU document provides a valuable basis for an updated review, with a supplementary search made for the years 1990–1993 and some improvements in the search strategy (e.g. by including text searching). A wider range of sources was also searched to determine whether there were trials of medical therapy which have been missed. This included searches of EMBASE and drugs databases. Additional searches were required to locate papers covering health-related quality of life issues (e.g. return to work) and patient preferences. In this area, the SBU search relied only on MEDLINE search headings which are not always accurate.

Conclusion

Although the RAND and SBU reviews can be criticised in terms of the limitations in their searches and in the issues they addressed, they are of an acceptable standard to provide a useful starting point for the current review of effectiveness of CABG and PTCA and medical therapy.

Quality assessment of the study (Gunnell & Smith, 1994)

This quality assessment was carried out by two CRD reviewers; it has been previously published in the NHS CRD DARE database from which it has been copied directly.

Authors' objectives

- To summarise the current research of the effectiveness and cost-effectiveness of different techniques for the investigation and treatment of coronary artery disease
- to highlight gaps in the research record
- to address specific issues surrounding the performance of coronary angiography and PTCA in units without cardiac surgical standby.

Participants and specific interventions

Patients with a diagnosis of angina, unstable angina or coronary disease, undergoing CABG surgery, PTCA and drug treatment were included in the review. The newer PTCA techniques (atherectomy and intracoronary stents) were also included.

Outcome assessed

Effectiveness in terms of patient mortality and morbidity and cost-effectiveness was assessed in the review.

Designs of included studies

The review included evaluations of RCTs, retrospective observational cohort studies and prospective observational cohort studies.

Sources searched

In order to identify primary studies, MEDLINE was searched from 1990 to 1993 (the keywords used in the search are given in the paper). Papers published before 1990 were identified from two literature reviews published by the RAND organisation in 1991 and from papers found through the MEDLINE search. Key journals were also handsearched from July 1993 to June 1994.

Assessment of study validity (or quality)

The only stated criteria for inclusion was that the studies were listed on MEDLINE and retrieved using the keywords: coronary disease, angina, unstable angina, PTCA and CABG.

The study did not specify:

- the method of applying the inclusion criteria
- how judgements of study validity (or quality) were made
- the method of extracting the data from primary studies.

Studies included

Seven RCTs and four observational cohort studies comparing CABG and PTCA were included. Two of the RCTs evaluated atherectomy and two compared intracoronary stents with PTCA.

The studies were combined in narrative review with more weight given to studies with a randomised design. They were listed according to whether they had a randomised or non-randomised design.

Results of the review

Effectiveness of treatment

No RCT had been performed in which all three treatments for IHD – CABG, PTCA and medical treatment – were compared. CABG provided improved angina relief compared with drug treatment and may prolong life in patients with more severe illness. PTCA was also better than drug treatment but less effective than CABG. Repeat intervention for return of symptoms was more frequently required after PTCA but increasing numbers of patients were also undergoing second and third repeat CABG for graft occlusion in the years after the original operation. Atherectomy was no more effective and was more expensive than conventional balloon angioplasty. Intracoronary stents reduced (in the short term) the problems associated with vessel occlusion after PTCA and, thus, the need for further intervention.

Service delivery issues

PTCA should not be performed without ready access to cardiothoracic support.

Gaps in the research

Further research is required which compares CABG and modern medical management of angina in those for whom CABG has not already been shown to prolong life.

Cost information

The short-term costs to the health service of PTCA were lower than CABG (£6916 versus £8739), although it has not been shown to be more cost-effective than CABG. An economic evaluation from a large RCT was expected to be available shortly. Hospital costs for atherectomy were significantly greater ($11,904 versus $10,637) than for angioplasty and there was little difference in 6-month event-free survival between them.

Authors' conclusions

Techniques for the management of IHD are developing rapidly and service expansion is occurring without trial evidence. More research is needed to determine the optimum balance of PTCA, CABG and the role of the newer angioplasty techniques. In the meantime, in the absence of long-term evidence of the superior cost-effectiveness of PTCA compared with CABG, the rapid expansion of this procedure should be limited. Where PTCA is carried out it should not be performed without ready access to cardiothoracic support. Patients should be fully informed of the benefits and disadvantages of CABG and PTCA when either procedure is indicated to enable them to make fully informed choices.

Commentary

This document is a very useful review of the most recent RCT evidence concerning treatments for IHD. It highlights the importance of not purchasing new technologies unless they have been evaluated by an RCT. It is not clear, however, whether all available studies were included in the review as the search was very limited.

Criteria for assessing the quality of systematic reviews

This was based on the checklist used to determine whether systematic reviews are entered on the NHS database DARE. Six criteria are used; if the review is poor for one or more of these, it is rejected.

1. Does the review answer a well defined question?
2. Was a substantial effort made to search for all the relevant literature?
3. Are the inclusion/exclusion criteria reported and appropriate?
4. Is the validity (quality) of the included studies adequately assessed?
5. Is sufficient detail of the individual studies presented?
6. Have the primary studies been combined or summarised appropriately?

Appendix 2

Search terms used to identify relevant literature

These terms were developed for MEDLINE. Some changes were required for some of the other databases searched.

Clinical effectiveness

Set	Description
S1	ANGINA
S2	"ANGINA PECTORIS"
S3	S1 OR S2
S4	"NITRATES"
S5	NITRATE?
S6	BETA(W)BLOCKER?
S7	"ADRENERGIC BETA-AGONISTS"
S8	CALCIUM CHANNEL BLOCKER?
S9	CALCIUM()CHANNEL()BLOCKER?
S10	"CALCIUM CHANNEL BLOCKERS"
S11	S4:S8
S12	S11 OR S10
S13	CORONARY ARTERY BYPASS
S14	CABG
S15	PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY
S16	PERCUTANEOUS()TRANSLUMINAL() CORONARY()ANGIOPLASTY
S17	PTCA
S18	ANGIOPLASTY
S19	ATHERECTOMY
S20	STENTS
S21	"MYOCARDIAL REVASCULARIZATION"
S22	"ANGIOPLASTY–ADVERSE EFFECTS–AE"
S23	"ANGIOPLASTY"
S24	"BALLOON DILATATION"
S25	"ANGIOPLASTY, LASER"
S26	"STENTS"
S27	S13 OR S14
S28	S16:S21
S29	S23:S26
S30	S27:S29
S31	"EVALUATION STUDIES"
S32	DT=RANDOMIZED CONTROLLED TRIAL
S33	"RANDOMIZED CONTROLLED TRIALS"
S34	"RANDOM ALLOCATION"
S35	"DOUBLE-BLIND METHOD"
S36	"SINGLE-BLIND METHOD"
S37	DT=CLINICAL TRIAL
S38	"CLINICAL TRIALS"
S39	CLINICAL(5W)TRIAL
S40	(SINGL? OR DOUBL? OR TREBL? OR TRIPL?)(5W)(BLIND? OR MASK?)
S41	"PLACEBOS"
S42	PLACEBO? OR RANDOM?
S43	"RESEARCH DESIGN"
S44	"COMPARATIVE STUDY"
S45	"FOLLOW-UP STUDIES"
S46	"PROSPECTIVE STUDIES"
S47	CONTROL? OR PROSPECTIV? OR VOLUNTEER?
S48	S31:S47
S49	REGIST?
S50	"REGISTRIES"
S51	S49 OR S50
S52	"COSTS AND COST ANALYSIS"
S53	"COST-BENEFIT ANALYSIS"
S54	"COST SAVINGS"
S55	"COST OF ILLNESS"
S56	"ECONOMICS"
S57	S56 AND S31
S58	COST()BENEFIT()ANALYSIS/TI,AB,SH
S59	COST()BENEFIT()ANALYSIS/TI,AB
S60	COST()BENEFIT/TI,AB
S61	COST()(EFFECTIVE? OR UTILITY)/TI,AB
S62	COST
S63	S62 AND S3
S64	COST()(SAVING OR MINIMIZATION OR MINIMISATION)/TI,AB
S65	"ECONOMICS, PHARMACEUTICAL"
S66	QALY
S67	QUALITY()ADJUSTED()LIFE() YEAR/TI,AB
S68	ECONOMIC
S69	ANALYSIS OR EVALUATION
S70	S68 AND S69
S71	BENEFIT OR EFFECTIVE?
S72	S71 AND S62
S73	S72 AND S56
S74	S72 AND S31
S75	EFFICACY OR RESPONSE OR SENSITIVITY
S76	S75 AND S62
S77	SPECIFICITY OR OUTCOME
S78	S77 AND S62
S79	(S76 OR S78) AND S31
S80	(S76 OR S78) AND S56
S81	S53:S61,S63
S82	S64:S67,S70

S83	S73:S74
S84	S81:S83
S85	S79:S80,S84
S86	S12 OR S30
S87	S31 OR S48 OR S51 OR S85
S88	S3 AND S86 AND S87
S89	"ANIMAL"
S90	"HUMAN"
S91	S89 NOT (S89 AND S90)
S92	S88 NOT S91

Health-related quality of life

Set	Description
S1	"QUALITY OF LIFE" OR "QUALITY-ADJUSTED LIFE YEARS"
S2	"CORONARY DISEASE"
S3	"ANGINA PECTORIS"
S4	ANGINA/TI
S5	P
S6	"CORONARY ARTERY BYPASS"
S7	"ANGIOPLASTY"
S8	S2:S4
S9	S6:S8
S10	S2 OR S3 OR S4 OR S6 OR S7
S11	S1 AND S10
S12	S11/ENG,HUMAN
S13	QUALITY()OF()LIFE/TI
S14	S12/1982:1996
S15	S7 AND (S2 OR S3 OR S4)
S16	S2 OR S3 OR S4 OR S6 OR S15
S17	S1 AND S16
S18	S17/ENG,HUMAN
S19	S18/1982:1996

Patient preferences

Set	Description
S1	"ANGINA PECTORIS"
S2	WILLINGNESS()TO()PAY
S3	"QUALITY-ADJUSTED LIFE YEARS"
S4	UTILIT?
S5	VALUATION
S6	HEALTHY()YEAR?()EQUIVALENT?
S7	S2-S6
S8	S2-S6
S9	UTILIT?/TI
S10	S2,S3,S5,S6,S9
S11	S1 AND S10
S12	S11/ENG,HUMAN
S13	RD S12 (unique items)
S14	QALY? OR (QUALITY()ADJUSTED()LIFE()YEAR?)
S15	S1 AND S14
S16	S13 OR S15
S17	RD S16 (unique items)

Cost and cost-effectiveness[1]

Set	Description
S1	"ANGINA PECTORIS"
S2	"ANGIOPLASTY, TRANSLUMINAL, PERCUTANEOUS CORONA"
S3	"CORONARY ARTERY BYPASS"
S4	S1 OR S2 OR S3
S5	"COSTS AND COST ANALYSIS"
S6	"COST-BENEFIT ANALYSIS"
S7	ECONOMIC()(EVALUATION OR ANALYSIS)/TI
S8	COST()EFFECTIVE?/TI
S9	"HOSPITAL COSTS"
S10	HEALTH RESOURCES
S11	"HEALTH RESOURCES"
S12	S5-S9,S10
S13	S5-S9,S11
S14	S4 AND S13
S15	S14/HUMAN, ENG
S16	S3-S11
S17	DT="LETTER"
S18	DT="EDITORIAL"
S19	S16-S18
S20	S15 NOT S19
S21	S20/1985-1991
S22	S21 (unique items)

[1] The search for economic studies within the clinical search was considered insufficintly detailed, so a specific search strategy was developed.

Appendix 3

Papers identified, rejected and reviewed

Clinical effectiveness – numbers of papers found

Database	Date of search	Result of search	Papers obtained	Number rejected	Number accepted for review
MEDLINE	8/96	1052 1967 1343			
MEDLINE Total		4362	665	541	124
EMBASE	9/96	248 482			
EMBASE total		730	31	29	2
DHSS data	8/96	6 40			
DHSS data total		46	0	–	–
Cochrane database	7/96	3	0	–	–
Dissertation Abstracts	23/7/96	10	0	–	–
Health Planning and Administration	23/7/96	2	0	–	–
Social Science Citation Index	23/7/96	0	–	–	–
Other sources		12	12	1	11
Subtotal		**5165**	**708**	**571**	**137**
Updated search	1/97	250	20	9	11
Total		**5415**	**728**	**580**	**148**

Note: In addition, a further 13 were identified in an update search at the end of 1997 and from comments by the Expert Panel.

Clinical effectiveness – reasons for rejection: surgical interventions

Reason	Number of papers
Non-randomised, non-UK-based, clinical trials with < 1000 subjects	
USA and Canada	26
Europe	11
Other	2
Non-randomised, non-comparative, UK-based, clinical trial with < 1000 subjects	1
Results already included from other papers	9
Papers included in SBU or RAND	12
Paper or article not applicable to review	10
Review article	4
Pre-1982 papers	1
Surgery total	**76**

Clinical effectiveness – reasons for rejection: medical interventions

Reason	Number of papers
Not between-class comparison of drug therapies	363
Between-class comparison but not RCT with > 6 months follow-up	141
Medical total	**504**

Health-related quality of life and patient preferences – numbers of papers found

Database	Date of search	Result of search	Papers obtained	Number rejected	Number accepted for review
MEDLINE and Health and Administration	10/96	227	40	19	21*

* *In addition, three HRQoL papers were identified during the clinical search making 24 papers reviewed in total.*

Health-related quality of life and patient preferences – reasons for rejection

Reason	Number of papers
No formal HRQoL instrument used	9
Not an empirical study	4
Angina patients together; no comparison of interventions	4
Not angina patients alone	1
Repeat publication	1
Total	**19**

Cost and cost-effectiveness – numbers of papers found

Database	Date of search	Result of search	Papers obtained	Number rejected	Number accepted for review
MEDLINE and Health and Administration	12/96	211	60	36	24*
Office of Health Economics	2/97	9	2	2	0
NHS CRD database	8/96	0	0		

* *In addition, one paper was identified during the clinical search.*

Cost and cost-effectiveness – reasons for rejection

Reason	Number of papers
Not main intervention/technology	15
Not comparative and non-UK	14
Not empirical paper	6
Charges rather than costs reported	2
Not angina	1
Total	**38**

Appendix 4

Summary tables of medical therapy

Clinical effectiveness

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Destors, *et al.*, 1989 France	Patients with stable angina pectoris RCT, multicentre 191 patients	Calcium channel blocker (bepridil) (78) vs. beta-blocker (propranolol) (78) vs. placebo (35)	Male: bepridil 64%, propranolol 73%, placebo 57%. Age (years): bepridil 54, propranolol 56, placebo 56. Previous MI: bepridil 31%, propranolol 33%, placebo 37%.	6 months
Loaldi, *et al.*, 1991 Italy	Patients with untreated stable angina, ≥ 50% stenosis major coronary artery RCT 80 patients	Beta-blocker (propranolol) 80 mg q.d.s. (40) vs. nitrate (ISDN) 40 mg b.d. (40)	Male: propranolol 77.5%; ISDN 82.5%. Age (years): propranolol 48; ISDN 51. Mean number stenoses per patient (SD): propranolol 2.0 (0.9); ISDN 2.1 (0.9). Duration of angina (months) (SD): propranolol 5.9 (1.4); ISDN 6.7 (1.3).	2 years
Vliegen, *et al.*, 1991 The Netherlands	Patients with stable angina pectoris for at least 3 months RCT, multicentre 56 patients	Calcium channel blocker (diltiazem) 120 mg b.d. (30) vs. beta-blocker (metoprolol) 100 mg b.d. (26)	Not recorded.	32 weeks

Study	Effectiveness	Adverse events	Authors' conclusions
Destors, *et al.*, 1989 France	Increased exercise duration, % (SD): placebo 8 (6.8); bepridil 31 (7.6); propranolol 24 (7.4); $p < 0.05$ vs. placebo. Increased workload % (SD): placebo 14 (7.1); bepridil 25 (8.0); propranolol 30 (9.8); $p = 0.05$ vs. placebo. No significant difference between drug groups.	Deaths (MI): placebo 0; bepridil 1; propranolol 1. Deaths (CVA): placebo 0; bepridil 0; propranolol 1. Severe coronary events (including cardiac death): placebo 6%; bepridil 8%; propranolol 10%. Non-cardiac adverse events (hypotension, hypoglycaemia, bronchospasm, allergy, fatigue, GI problems, psychiatric problems): placebo 6; bepridil 9; propranolol 23 (including 14 fatigue, 10 GI problems); $p = 0.003$.	Both agents failed to show a strong beneficial effect compared with placebo, after 6 months of treatment.
Loaldi, *et al.*, 1991 Italy	Progression of disease (vessel narrowing): stenoses per patient (SD): ISDN 2.1 (0.9) increasing to 2.4 (0.8); propranolol 2.0 (0.9) increasing to 2.3 (0.5); change, not significant (NS). Patients with progression of disease at follow-up: ISDN 48%, propranolol 70%; $p < 0.05$. Patients with steadiness of disease: ISDN 45%; propranolol 23%; $p < 0.05$. Infarction rate: ISDN 1; propranolol 3; p, NS.	Not reported.	Propranolol showed an adverse influence on coronary atherosclerosis with reference to the evolution of both > 50% and < 50% narrowings but not to the formation of new stenoses.
Vliegen, *et al.*, 1991 The Netherlands	Exercise tolerance: Increase in duration of exercise (min): diltiazem 0.3; metoprolol 0.2; p, NS.	Not reported.	Monotherapy with diltiazem is at least as effective as therapy with metoprolol.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Boberg, *et al.,* 1992 (VISACOR Study Group) Sweden	Patients with stable angina pectoris suitable for treatment with beta-blockers RCT, multicentre 173 patients	Beta-blocker with ISA (epanolol) 200 mg (114) o.d. vs. beta-blocker (atenolol) 100 mg o.d. (59)	Male: 85%. Mean age (SD): 58 years (7.1). Exercise tolerance (SD): atenolol 652 seconds (27); epanolol 707 seconds (20).	1 year
Kawanishi, *et al.,* 1992 USA	Patients with stable angina pectoris RCT 74 patients	Beta-blocker (propranolol) (21) vs. calcium channel blocker (nifedipine) (16) vs. combination (32)	Male: 66%. Mean age (SD): 54 years (7). NYHA angina class: I 4%; II 73%; III 23%. EF (SD): 0.62 (0.13).	6 months
Nahrendorf, *et al.,* 1992 Germany	Patients with stable angina pectoris RCT 31 patients	Vasodilating beta-blocker (carvedilol) (21) vs. beta-blocker/nitrate (propranolol/ISDN) combination (10)	Male: 100%. Mean age: 54 years.	6 months

Study	Effectiveness	Adverse events	Authors' conclusions
Boberg, *et al.,* 1992 (VISACOR Study Group) Sweden	Exercise tolerance: Total exercise duration at 1 year, seconds (SD): atenolol 700 (17); epanolol 718 (12); NS. Median angina attack rate in 1st month, days: atenolol 0.15; epanolol 0.24; NS. Median angina attack rate for whole period, days: atenolol 0.15; epanolol 0.17; NS. VAS scores for (4/52 weeks), mm: Energy: atenolol 50/50; epanolol 55/55; NS between groups, NS over time. Well-being: atenolol 54/53; epanolol 58/58; NS between groups, NS over time. Activity: atenolol: 52/52; epanolol 56/56; NS between groups, NS over time. Warm hands/feet: atenolol 56/57; epanolol 63/63; $p < 0.05$ between groups, NS over time.	ADRs reported: atenolol 24%; epanolol 9%; $p < 0.005$. Withdrawal rates, %: Worsening angina: atenolol 0; epanolol 3.5. MI: atenolol 0; epanolol 4.4. ADR: atenolol 13.5; epanolol 3.5; $p < 0.01$. Other: atenolol 3.4; epanolol 4.4.	Treatment with epanolol showed no SDs in efficacy compared with atenolol (judged by angina attack rate). Epanolol tended to be better tolerated with fewer adverse reactions than atenolol.
Kawanishi, *et al.,* 1992 USA	Angina frequency (episodes per week (SD)): Nifedipine 6.3 (4.3) reduced to 2.7 (5.6); propranolol 7.1 (5.8) reduced to 2.0 (2.3); nifedipine/propranolol 4.3 (7.9); propranolol/nifedipine 1.3 (1.7); $p < 0.05$ compared with baseline. Combination no greater increase than sole agents. Exercise tolerance (time, seconds (SD)): Nifedipine 342 (127) increased to 433 (132); propranolol 314 (157) increased to 433 (159); nifedipine/propranolol (and propranolol/ nifedipine) 435 (144); $p < 0.05$ compared with baseline. Combination no greater increase than sole agents.	Not reported.	Nifedipine or propranolol alone, titrated to individually maximally tolerated dosages, are equally effective in long-term control of painful and painless ischaemia, anginal episodes and exercise-induced ischaemia. Combination therapy further reduced only exercise-induced angina and maximal exercise-induced ST depression.
Nahrendorf, *et al.,* 1992 Germany	Exercise time (seconds): Carvedilol 321 increased to 409, $p < 0.01$; propranolol/ISDN 372 increased to 395. Time to ST segment depression (seconds): Carvedilol 240 increased to 360, $p < 0.01$; propranolol/ISDN 210 increased to 240.	Carvedilol: two reports (dizziness). Propranolol/ISDN: one report (postural hypotension).	Long-term anti-anginal and anti-ischaemic effects of carvedilol more marked than propranolol/ISDN.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Guermonprez, *et al.,* 1993 France	Patients with stable angina pectoris RCT, multicentre 123 patients	Calcium channel blocker (diltiazem) (63) vs. potassium channel activator (nicorandil) (60)	Male: diltiazem 86%; nicorandil 90%. Mean age, years: diltiazem 60.7; nicorandil 60.1. Duration of angina, months (SD): diltiazem 3.7 (0.5); nicorandil 3.6 (0.9).	3 months (see later study for follow-up)
Singh, 1993 USA	Patients with stable angina pectoris RCT, multicentre 80 patients	Calcium channel blocker (amlodipine) (40) vs. beta-blocker (nadolol) (40)	Male: amlodipine 88%; nadolol 90%. Mean age, years : amlodipine 65; nadolol 62. Duration of angina, months: amlodipine 79.8; nadolol 78.3.	28 weeks
Dargie, *et al.,* 1996 Fox, *et al.,* 1996 (TIBET study) Europe	Patients with stable angina pectoris RCT, multicentre 682 patients (NB: 608 satisfied inclusion criteria; analysis reports results for 682 patients, commenting that results for 608 group 'very similar')	Beta-blocker (atenolol) (226) vs. calcium channel blocker (nifedipine) (232) vs. combination (224)	Male: atenolol 87%, nifedipine 82%, combination 88%. Mean age, years: atenolol 59; nifedipine 60; combination 60. Previous MI, %: atenolol 34; nifedipine 31; combination 34. Diabetes, %: atenolol 4, nifedipine 3, combination 8. Previous PTCA, %: atenolol 2; nifedipine 2; combination 2. Previous CABG, %: atenolol 6; nifedipine 5; combination 4.	1–3 years

Study	Effectiveness	Adverse events	Authors' conclusions
Guermonprez, *et al.,* 1993 France	Exercise tolerance: NS between groups. Angina frequency: NS between groups.	38 reports. Diltiazem 30.2% (GI disorders 9.5%); nicorandil 31.7% (headache 22%).	Nicorandil and diltiazem have an equivalent safety and efficacy profile.
Singh, 1993 USA	Total exercise time, seconds: Amlodipine 454 increased to 462; nadolol 490 decreased to 475; NS between groups. Time to angina onset, seconds: Amlodipine 339 increased to 411; nadolol 393 increased to 424; NS between groups. ST segment depression: Amlodipine decreased by 9%, nadolol by 21%; NS between groups. Angina attack rate, per week: Amlodipine 4 decreased to 0.3; nadolol 3 decreased to 0.3; NS between groups.	Patients with side-effects, %: amlodipine 43; nadolol 83. Patients withdrawn due to side-effects, %: amlodipine 8; nadolol 10. Bradycardia, %: amlodipine 3; nadolol 40. Palpitations, %: amlodipine 10; nadolol 15. Peripheral oedema, %: amlodipine 10; nadolol 5. Dizziness, %: amlodipine 13; nadolol 25. Headache. %: amlodipine 23; nadolol 18.	The efficacy of amlodipine, 2.5–10 mg daily, is equivalent to nadolol, 40–160 mg daily, in patients with stable exertional angina pectoris.
Dargie, *et al.,* 1996 Fox, *et al.,* 1996 (TIBET study) Europe	Primary endpoints (severest endpoint reported for each patient): Cardiac death: atenolol 3; nifedipine 6; combination 4. Non-fatal MI: atenolol 14; nifedipine 15; combination 7. Unstable angina: atenolol 12; nifedipine 4; combination 8. CABG: atenolol 7; nifedipine 6; combination 4. PTCA: atenolol 1; nifedipine 0; combination 0. Treatment failure: atenolol 10; nifedipine 15; combination 8. NS between groups. Secondary endpoints: Time to onset of angina; total duration of exercise test; ischaemic episodes (see Fox, *et al.,* 1996).	Not reported.	All treatments equally reduced evidence of myocardial ischaemia either on exercise or on ambulatory monitoring. It is speculative to suggest that the combination reduces the frequency of unwanted endpoints but there appears to be a definite trend which could only be investigated further in a larger-scale study.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Fox, *et al.,* 1996 (TIBET study) Europe	Patients with stable angina pectoris RCT, multicentre 682 patients (NB: 608 satisfied inclusion criteria. Analysis reports results for 682 patients, commenting that results for 608 group 'very simila')	Beta-blocker (atenolol) (226) vs. calcium channel blocker (nifedipine) (232) vs. combination (224)	Male: atenolol 87%; nifedipine 82%; combination 88%. Mean age, years: atenolol 59; nifedipine 60; combination 60. Previous MI, %: atenolol 34; nifedipine 31; combination 34. Diabetes, %: atenolol 4; nifedipine 3; combination 8. Previous PTCA, %: atenolol 2; nifedipine 2; combination 2. Previous CABG, %: atenolol 6; nifedipine 5; combination 4.	1–3 years
Rehnqvist, *et al.,* 1996 (APSIS) Sweden	Patients with a clinical history of stable angina Double-blind RCT, multicentre 809 patients	Beta-blocker (200 mg metoprolol) (406) vs. calcium channel blocker (240 mg verapamil b.d.) (403)	Males: metoprolol 73%; verapamil 66%. Mean age, years: metoprolol 59; verapamil 59. Previous CABG/PTCA, %: metoprolol 5; verapamil 7. Ex-smokers, %: metoprolol 50; verapamil 36; $p < 0.001$. Diabetes, %: metoprolol 8; verapamil 9. Duration of angina, years: metoprolol 2; verapamil 2. NYHA class I, %: metoprolol 27; verapamil 25; NYHA class II, %: metoprolol 68; verapamil 69.	3 years

Study	Effectiveness	Adverse events	Authors' conclusions
Fox, *et al.,* 1996 (TIBET study) Europe	Primary endpoints: see Dargie, *et al.,* 1996. Secondary endpoints: Time to onset of angina, seconds (SD): Atenolol 128.0 (11.3); nifedipine 126.7 (15.0); combination 144.3 (13.7). Duration of treadmill exercise test, seconds: Atenolol 91.4 (10.0); nifedipine 90.5 (11.1); combination 98.0 (11.7). Patients with no ischaemic episodes after treatment (y) compared with before 6 weeks of treatment (x) – (y/x): Atenolol 44/89; nifedipine 40/87; combination 35/80.	Not reported.	Both medications alone and in combination caused significant improvements in exercise parameters and significant reductions in ischaemic activity; differences between groups, NS. In the management of mild chronic stable angina there appears to be little advantage in using combination therapy for ischaemia reduction.
Rehnqvist, *et al.,* 1996 (APSIS) Sweden	Deaths, %: metoprolol 5.4; verapamil 6.2. Non-fatal MI, %: metoprolol 4.2; verapamil 3.5. CABG, %: metoprolol 11; verapamil 9.7. PTCA, %: metoprolol 3; verapamil 1.2. Angiography without revascularisation, %: metoprolol 4.2; verapamil 5. Other unstable angina, %: metoprolol 0; verapamil 1.2. Cerebrovascular disease, %: metoprolol 2.7; verapamil 3.2. Peripheral vascular disease, %: metoprolol 0.7; verapamil 0.5.	Patients with side-effects, %: GI: metoprolol 10; verapamil 22. Neurological: metoprolol 22; verapamil 25. Cardiovascular: metoprolol 15; verapamil 16. Respiratory: metoprolol 3; verapamil 2. Other: metoprolol 4; verapamil 4. Total side-effects, %: metoprolol 13; verapamil 17. Withdrawn, %: metoprolol 11; verapamil 15; *p,* 0.13. Administrative withdrawals, %: metoprolol 20; verapamil 17.	Difference in treatment effects of metoprolol and verapamil on mortality and nonfatal cardiovascular events, NS. Both drugs are well tolerated.

Health-related quality of life

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Fletcher, *et al.,* 1988 UK	HRQoL assessment beside RCT of GTN transdermal patches vs. placebo in patients with chronic stable angina of > 3 months duration inadequately controlled by beta-blockers RCT, multicentre (270 general practices) 427 patients	GTN, 5 mg, transdermal patches (210) vs. placebo (217)	Male: 100%. Mean age, years (SD): GTN 60.5 (7.1); placebo 60.4 (7.8). Previous MI, %: GTN 39; placebo 48. Smokers, %: GTN 24; placebo 17. On beta-blockers, %: GTN 87; placebo 75. On beta-blockers and Ca antagonists, %: GTN 23; placebo 24. Mean SIP score (SD): Physical: GTN 6.8 (8.2); placebo 8.0 (8.2). Psychosocial: GTN 10.0 (12.0); placebo 12.1 (12.0).* Total: GTN 9.4 (8.9); placebo 11.5 (9.0).* Health Index: GTN 70.1 (19.8); placebo 66.3 (20.5).* * $p < 0.05$.	8 weeks
Blake & Lewis, 1992 UK	Assessment of patient preferences in cohort of patients from VISA I and II trials: VISA I – effectiveness of epanolol (beta-blocker with ISA) vs. metoprolol (standard beta-blocker); VISA II – effectiveness of epanolol vs. nifedipine (calcium channel blocker) Prospective RCT, crossover, multicentre 1179 patients (VISA I, 608; VISA II, 571)	Stable angina patients randomised to: Epanolol, 200 mg o.d., metoprolol, 100 mg b.d., or nifedipine SR, 20 mg b.d., for 4 weeks, then crossed over to other therapy for 4 weeks	VISA I: Male: 100%. Mean age: 74 years. Mean angina duration, 3.7 years. VISA II: Male: 663%. Mean age: 62.2 years. Mean angina duration: 4.2 years.	None

Study	Effectiveness	Adverse events	Authors' conclusions
Fletcher, *et al.,* 1988 UK	SIP with English weightings Health Index (from Fanshel, *et al.,* 1970).	1. Reduction in angina attack rate same for both groups. 2. Mean improvement in SIP (95% CI): Physical: GTN 0.3 (–0.2, 0.8); placebo 0.8 (0.4, 1.2). Psychosocial: GTN 0.7 (–0.2, 1.6); placebo 1.8 (0.9, 2.7).* Total: GTN 0.6 (0, 1.2); placebo 1.2 (0.6, 1.8).* Health Index: GTN –0.3 (–2.0, 1.3); placebo 0.1 (–1.8, 1.6). * $p < 0.05$.	The continuous use of 5 mg transdermal GTN offers no benefit over placebo in the treatment of angina. Quality-of-life measurements showed a significant adverse effect of active treatment, principally in the social interaction dimension of SIP.
Blake & Lewis, 1992 UK	Patients' elicited preferences	VISA I: Patients (total) 608; number evaluable 552. No preference, 28%; prefer epanolol, 39%; prefer other agent, 33%. *p,* 0.089. VISA II: Patients (total); number evaluable 490. No preference, 36%; prefer epanolol, 39%; prefer other agent, 25%. *p,* < 0.001.	Patients preferred epanolol to nifedipine and there is evidence of a preference for epanolol over metoprolol.

Cost and cost-effectiveness (model)

Study (per-spective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusions
Larratt, 1994 USA (Third party payer)	To examine the comparative costs of ISMN, 20 mg b.d., ISDN, 20 mg t.d.s., and GTN patches, 2.4 mg/day in the management of coronary artery disease (CEA)	Decision analytic model. Clinical and economic data pooled to derive cost per successfully treated patient for three treatments, using a theoretical 45–55-year-old man with newly diagnosed angina.	Clinical: process of care for each treatment derived from literature review and expert opinion. Probabilities obtained by expert opinion and 'confirmed' by literature, e.g. titration, tolerance, remission. Economic: resource use from expert opinion including results of treatment failure (other drugs, surgery). Sources: 1992, drugs database, HCFA.	12 months	Average annual healthcare cost: Patches: $6152 ISMN: $5193 ISDN: $7207 Average cost per successfully treated patient (total control of angina symptoms): Patches: $18,988 ISMN: $15,594 ISDN: $21,386	ISMN is more cost-effective than ISDN or patches in the treatment of stable angina. ISMN tolerance profile and lack of need for titration resulted in medical cost savings sufficient to offset its higher unit cost.

Appendix 5

Summary tables of medical therapy versus CABG

Clinical effectiveness

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Bhayana, *et al.,* 1980 USA	Patients with history of stable angina for 6 months, myocardial ischaemia or a positive stress test RCT, multicentre 146 patients	Groups: CABG (IMA) (71) vs. medical therapy (75)	1-vessel disease: 19% medical, 16% CABG. 2-vessel disease: 31% medical, 42% CABG. 3-vessel disease: 51% medical, 48% CABG. Left main disease: 8% medical, 7% CABG. EF ≥ 50%: 20% medical, 22% CABG. EF < 50%: 7% medical, 7% CABG. EF unknown: 73% medical, 70% CABG. Diabetes: 19% medical, 17% CABG. NYHA class III or IV: 64% medical, 76% CABG.	12 years Intention-to-treat
Palac, *et al.,* 1981 USA	Patients with surgically bypassable chronic stable coronary artery disease RCT 148 patients	Groups: medical therapy (77) vs. CABG (71)	Original study included other subgroups of patients in baseline characteristics.	5 and 10 years
Frick, *et al.,* 1983 Finland	Male patients under 65 years old with stable angina, despite medical treatment, and significant coronary artery stenosis in at least two arteries suitable for CABG RCT 100 patients	Groups: medical therapy (50) vs. CABG (50)	2-vessel disease: 20% medical, 29% surgical. 3-vessel disease: 80% medical, 71% surgical. Left main stenosis: 16% medical, 11% surgical. Mean age, years: 47 medical, 46 surgical. EF: 67% medical, 66% surgical. Previous MI: 28% medical, 49% surgical. NYHA functional class: 3.4 medical, 3.4 surgical.	5 years Only re-examined patients included 14 (28%) medical patients and 8 (16%) CABG excluded from analysis
Gersh, *et al.,* 1985 (for CASS participants) USA	Patients over 65 years who underwent arteriography; no previous CABG Multicentre, CASS registry 1491 patients	Groups: medical therapy (630) vs. CABG (861)	Male: 69% medical, 74% CABG, $p < 0.04$. 3-vessel disease: 44% medical, 59% CABG, $p < 0.0001$. Age ≥ 75 years: 7% medical, 4% CABG, $p = 0.04$. EF < 0.5: 32% medical, 22% CABG, $p = 0.0003$. Unstable angina: 41% medical, 58% CABG, $p < 0.0001$. Angina class III or IV: 56% medical, 75% CABG, $p < 0.0001$.	10 years

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	Long-term MI rate	CABG	Conclusions
Bhayana, *et al.,* 1980 USA	Operative mortality: 8 (12%)	59% medical, 58% CABG				Study shows CABG produces no measurable improvement in survival. This operation should have been subjected to a prospective RCT considerably earlier.
Palac, *et al.,* 1981 USA		5 years: 31% medical, 13% CABG. 10 years: 47% medical, 31% CABG.			21% crossed over from medical to CABG.	Surgical therapy at 10 years causes higher incidence of disease progression in native coronary arteries proximal to insertion of graft regardless of patency.
Frick, *et al.,* 1983 Finland		20% medical, 4% CABG. Annual mortality: 4% medical, 0.8% CABG, $p < 0.05$.	Mean score: 1-year – 3.5 medical, 1.8 CABG; 5-year – 3.2 medical, 1.9 CABG.			CABG found to reduce morbidity and mortality, and improve employment rates compared with randomly designed medical control group.
Gersh, *et al.,* 1985 (for CASS participants) USA		6-year survival (adjusted): 64% medical, 79% CABG, $p < 0.0001$. 2-vessel disease: 70% medical, 89% CABG, $p < 0.0001$. 3-vessel disease: 47% medical, 75% CABG, $p < 0.0001$.	Free from chest pain: 29% medical, 62% CABG.		11% of medical group had CABG.	Within limits of registry database and applicability of current statistical techniques, findings suggest that CABG may prolong survival in selected higher-risk patients aged 65 yearsor older. Such patients are less amenable to randomisation.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Takaro, *et al.*, 1985 USA	Patients with left main disease RCT, multicentre 91 patients	Groups: CABG (48) vs. medical therapy (43)	See other VA studies.	42 months Intention-to-treat
Alderman, *et al.*, 1990 (for CASS investigators) USA	Patients, 65 years old or less, with angina class I or II, EF > 0.35, and with operable coronary vessels containing lesion(s) of ≥ 70% of diameter RCT, multicentre 780 patients (from registry of 24,959, of whom 2099 eligible for trial).	Groups: medical therapy (390) vs. CABG (390)	1-vessel disease: 27% medical, 27% CABG. Age > 53 years: 42% medical, 42% CABG. Age < 47 years: 26% medical, 24% CABG. EF ≥ 0.5: 73% medical, 75% CABG. No angina: 22% medical, 22% CABG. NHYA angina class I: 12% medical, 17% CABG. NHYA angina class II: 62% medical, 56% CABG.	10 years Intention-to-treat
VA Coronary Artery Bypass Surgery Cooperative Study Group, 1992 USA	Patients with stable angina, ≥ 1 major coronary artery with ≥ 50% stenosis and graftable distal segment RCT, multicentre 434 patients	Groups: medical therapy (217) vs. CABG (217)	Mean age, years: 51 medical, 51 surgical. NYHA III or IV: 58% medical, 59% surgical. History of MI: 58% medical, 63% surgical. Hypertension history: 30% medical, 28% surgical. 1-vessel disease: 14% medical, 15% surgical. 2-vessel disease:31% medical, 32% surgical. 3-vessel disease: 56% medical, 53% surgical. Left main disease: 12% medical, 14% surgical. EF < 50%: 35% medical, 31% surgical.	15 years Intention-to-treat

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	Long-term MI rate	CABG	Conclusions
Takaro, *et al.*, 1985 USA	Operative mortality: 3 (6.5%)	Survival: 65% (medical 88%, surgical 50–75%). Stenosis: 82% medical, 92% surgical. > 75% stenosis: 48% medical, 83% surgical, $p = 0.036$. Impaired LVF: 62% medical, 90% surgical, $p = 0.05$.		Nonfatal: 15% medical, 24% surgical.		Study supports evidence that survival significantly better with surgical therapy for patients with left main disease, particularly those with severe arterial narrowing, associated right coronary disease, impaired LVF and multiple clinical risk factors. Some subgroups of patients with left main disease have good prognosis with medical treatment but results based on such small numbers that there is no strong evidence that surgery is not beneficial.
Alderman, *et al.*, 1990 (for CASS investigators) USA	Operative mortality: 1.4%.	5-year survival: 92% medical, 95% CABG. 10-year survival 79% medical, 82% CABG.		At 10 years alive and free from MI: 69% medical, 66% CABG.	Crossover to CABG: 10%. No CABG: 2%.	CASS results continue to suggest that for patients with mild angina and normal LVF a strategy of initial medical therapy does not impose a long-term penalty in terms of survival or non-fatal MI. If symptoms progress or medication unacceptable surgical revascularisation may be required.
VA Coronary Artery Bypass Surgery Cooperative Study Group, 1992 USA		18-year survival: 33% medical, 30% CABG, *p*, NS. 7-year survival: 70% medical, 77% CABG, $p = 0.04$.	Angina-free – at 5 years: 4% medical, 12% CABG, $p < 0.001$. – at 10 years: 6% medical, 5% CABG, $p < 0.001$. – at 15 years: 3% medical, 4% CABG.	At 15 years – free from MI: 59% medical, 51% CABG. – free from non-fatal MI: 68% medical, 56% CABG, $p = 0.015$.		No significant differences in survival, in relief of angina, or in post-MI mortality between patients assigned to medical or surgical therapy. Medically assigned patients continued to have significantly lower rates of non-fatal MI or death at 18 year follow-up.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Manske, *et al.*, 1992 USA	Insulin-dependent diabetic patients, lesions suitable for revascularisation, left ventricular EF > 0.35, atypical chest pain or no pain RCT 26 patients	Groups: medical therapy (13) vs. CABG (13)	Male: 46% medical, 46% revascularisation. Mean number arteries > 50% stenosis: 2.4 medical, 2.7 revascularisation. Mean age, years: 41 medical, 40 revascularisation. EF: 0.57 medical, 0.56 revascularisation. Mean age at diabetes onset, years: 13 medical, 11 revascularisation.	5 years ECG every 3–6 months Intention-to-treat
Muhlbaier, *et al.*, 1992 USA	Patients with significant coronary artery disease Cohort 3824 patients	Groups: medical therapy (2857) vs. CABG (2967)	Males: 80% medical, 82% surgical, $p = 0.08$. 1-vessel disease: 33% medical, 13% surgical. 2-vessel disease: 28% medical, 27% surgical. 3-vessel disease: 35% medical, 45% surgical. Left main disease: 4% medical, 15% surgical, $p < 0.001$. Mean age, years: 54 medical, 54 surgical, $p < 0.001$. EF: 53% medical, 56% surgical, $p < 0.001$. Diabetes: 15% medical, 14% surgical, $p = 0.09$. NYHA class III or IV: 77% medical, 86% surgical, $p < 0.001$. Unstable angina: 10% medical, 18% surgical, $p < 0.001$.	15–20 years

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	Long-term MI rate	CABG	Conclusions
Manske, *et al.*, 1992 USA		Death from MI: 3/13 medical, 0/13 revascularisation.	Unstable angina: 1/13 medical, 0/13 revascularisation	Non-fatal MI: 6/13 medical, 2/13 revascularisation	Secondary CABG: 6/13 medical, 2/13 revascularisation	When insulin-dependent diabetics being assessed for renal transplantation are found to have symptomless coronary artery stenoses, > 75% revascularisation may decrease incidence of MI. These results should be interpreted with caution as most of these patients had juvenile-onset diabetes.
Muhlbaier, *et al.*, 1992 USA		Event-free survival – at 3 years: 77% medical, 80% surgical. – at 5 years: 69% medical, 75% surgical. – at 10 years 54% medical, 57% surgical. – at 15 years 43% medical, 42% surgical. 10-year EF > 50%: 65% medical, 74% surgical. EF 35–50%: 50% medical, 62% surgical. EF < 35%: 27% medical, 46% surgical.		10-year EF > 50%: 41% medical, 49% surgical. EF 35–50%: 26% medical, 26% surgical. EF < 35%: 5% medical, 11% surgical.		This study demonstrates that modern surgical therapy significantly reduces coronary heart disease events for many patients with IHD.

continued

Health-related quality of life

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Rogers, *et al,* 1990 (CASS study) USA	HRQoL assessment beside RCT of medical therapy vs. CABG RCT, multicentre 780 patients	CABG (390) vs. medical therapy (390) of angina with > 70% diameter stenosis in one or more operable coronary arteries	Reported elsewhere (CASS investigators 1981; 1983). 144 medical patients subsequently had CABG in the next 10 years. Group A: mild angina (CHA Class I or II) and normal LVF (514). Group B: mild angina (CHA Class I or II) and moderately impaired LVF (106). Group C: free of angina after MI (160).	9.0–13.1 years (mean 11 years)

Study	Instruments used	Results			Conclusions
Rogers, *et al,* 1990 (CASS study) USA	Symptomatology Activity level Employment Hospitalisation Smoking status	1. Chest pain (% free from)	Medical*	CABG	This study demonstrates that improvements in quality-of-life indices observed in surgically assigned patients during the first 5 years after entry appear to be greatly attenuated by 10 years, unless patients who go on to surgery are excluded.
		At entry	22	22	
		At 1 year	30	66	
		At 5 years	38	63	
		At 10 years	42	47 (p-values not reported)	
		*(includes 144 medical patients who went on to have surgery)			
		Censored analysis (removed medical patients who had surgery)			
		At 10 years:			
		Groups A and B	18	38 ($p < 0.001$)	
		Group C	28	53 ($p < 0.002$)	
		2. Heart failure (% absent in) censored analysis*			
		At 10 years	42	62 ($p < 0.0001$)	
		3. Activity limitation (% free of) censored analysis*			
		At entry	15	18	
		At 10 years	13	30 ($p < 0.001$)	
		4. Employment (% in) censored analysis*			
		At entry	69	76	
		At 10 years	17	29 ($p < 0.001$)	
		5. Recreation (% taking part in moderate exertion) censored analysis*			
		At 10 years	13	22 ($p = 0.003$)	
		6. Hospitalisation			
		Number of days hospitalised per 1000 patient days	6.7	9.7 ($p < 0.0001$)	
		Excluding admission for surgery	6.7	6.1 ($p < 0.0001$)	
		* Uncensored analysis: no difference			

Cost and cost-effectivness (primary data)

Study	Design	Baseline characteristics	Selection criteria
Charles *et al.,* 1982 USA	Prospective cost-analysis alongside CASS RCT	Mean age, years: 51.1 (medical), 52 (surgical) Female, %: 12.2 (medical), 12.3 (surgical) Risk factors, %: hypertension – 26.2 (medical), 19.5 (surgical) diabetes – 3.6 (medical), 4.9 (surgical) smoking – 78.6 (medical), 69.5 (surgical) elevated triglyceride level – 21.4 (medical), 13.4 (surgical) elevated cholesterol level – 41.7 (medical), 41.5 (surgical) Unstable angina, %: 19 (medical), 14.6 (surgical) Mean number of diseased vessels: 2.3 (medical), 2.4 (surgical)	Patients in CASS study (see pages 91–92)

Study	Costing methods	Follow-up (duration of costing)	Results	Conclusions
Charles *et al.,* 1982 USA	Perspective: partial health service (hospital). Patients included: all from one centre in trial. Based on hospital charges; includes hospital, clinician, outpatient fees; exclusions not detailed. Expressed in 1979 US$.	1 year	Mean hospital charges, $ (SD): CABG (n = 74) 8068 (2300); medical (n = 82) 2618 (1943); late surgical (n = 10) 10,319 (3082). Professional charges, $ (SD): CABG 3032 (776); medical 814 (280); late surgical 3235 (879). Mean total charges for 1 year, $ (SD): CABG 11,100 (2899); medical 3432 (2062); late surgical 13,554 (3845). $p < 0.05$: medical costs significantly lower than surgical and late surgical costs.	Hospital charges significantly higher in first year for surgical patients and late surgical patients compared with medical patients.

Cost and cost-effectivness (model)

Study (per-spective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusions
Weinstein, & Stason, 1982 USA (Third party payer)	To examine the cost-effectiveness of CABG vs. medical therapy (propranolol, 320 mg/day, Isordil®, 120 mg/day, GTN, 10 tablets/week) in patients with symptomatic coronary artery disease. (CUA)	1. Clinical and economic data pooled to derive cost per QALY for theoretical 55-year-old man with 1-, 2-, 3-vessel or left main disease, and normal or poor LVF. 2. Attitude to risk of surgical death analysed. 3. Sensitivity analysis to test assumptions.	Clinical: operative mortality from ECSS, VA and other studies. Data 'pooled' (method not reported). Patients with poor LVF: one clinical series. Survival after surgery and medical management: VA, ECSS and ten CABG observational studies; 6-year follow-up data used. Life expectancies taken from US life tables. 'Symptom relief' from ECSS. No difference assumed after 10 years. Attitudes to risk: Y^r from 0.5–1.0 to examine fear of operative mortality. Economic: charges from Medicare, MI, re-operation rates from trials (1981 US$)	Life span of theoretical cohort. Costing for 10 years, annual discount rate: 5%.	Incremental cost-effectiveness ratio for CABG over medical (incremental cost per additional QALY/$ of CABG over medical ($): left main disease: 3800; 1-vessel disease: 30,000; 2-vessel disease: 17,500; 3-vessel disease: 7200. 3-vessel disease + poor LVF: 10,500. Sensitivity analysis: Evidence of quality-of-life changes important in 1-vessel disease. Use of VA data made CABG less cost-effective.	For patients with severe angina, estimated net incremental cost per QALY from CABG ranges from $3800 in left main disease to $30,000 in 1-vessel disease. These figures compare favourably with those for other accepted medical therapies such as treatment of moderate diastolic hypertension.
Williams, 1985 UK (NHS)	To assess cost-effectiveness of CABG over medical therapy in differing severities of angina, compared with other costly therapeutic technologies (CUA).	Clinical and economic data pooled to derive cost per QALY for theoretical 55-year-old man with 1-, 2-, 3-vessel or left main disease and normal LVF, for mild, moderate and severe angina. Also PTCA in 1-vessel disease.	Clinical: quality of life and increased life expectancy values from three cardiologists, to give expected increased QALYs of CABG over medical therapy. Economic: costs from DHSS 1983/84, rates of repeat procedures from Weinstein, *et al.,* 1982.	Life span of theoretical cohort; costing period not clear.	Incremental cost-effectiveness ratio for CABG over medical (cost per QALY/1000 (£)) for mild/moderate/severe angina: left main disease – 2.52/1.33/1.04; 1-vessel disease – –/12.00/11.40; 2-vessel disease – 12.60/4.00/2.28; 3-vessel disease – 6.30/2.40/1.27. No sensitivity analysis reported; no ranges reported.	Resources should be redeployed at margin for which benefits are high in relation to costs, such as, CABG for severe angina with left main disease and 3-vessel disease, and moderate angina with left main disease.

Appendix 6

Summary tables of medical therapy versus PTCA

Clinical effectiveness

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Pepine, *et al.*, 1994 (for ACIP investigators) USA	Patients with angiographic evidence of coronary artery disease suitable for revascularisation and abnormal stress test RCT, multicentre 618 patients	Groups: angina-guided medical strategy (204) vs. ischaemia-guided medical strategy (202) vs. revascularisation (212)	Male, %: 89 angina, 85 ischaemia, 81 revascularisation. 1-vessel disease, %: 23 angina, 25 ischaemia, 24 revascularisation. Mean age, years: 61 angina, 62 ischaemia, 61 revascularisation. White, %: 87 angina, 85 ischaemia, 88 revascularisation. EF ≥ 65%: 47% angina, 42% ischaemia, 45% revascularisation. Prior revascularisation, %: 24 angina, 22 ischaemia, 19 revascularisation. Diabetes, %: 14 angina, 18 ischaemia, 19 revascularisation.	12 weeks and 1 year Intention-to-treat
Davies, *et al.*, 1997 USA (ACIP 2-year follow-up)	See above 558 patients	Groups: angina-guided medical strategy (183) vs. ischaemia-guided medical strategy (183) vs. revascularisation by CABG or PTCA (192)	Male, %: 90 angina, 85 ischaemia, 83 revascularisation. 1-vessel disease, %: 22 angina, 25 ischaemia, 26 revascularisation. Mean age, years: 61 angina, 62 ischaemia, 61 revascularisation. EF ≥ 65%: 48% angina, 42% ischaemia, 46% revascularisation. Prior revascularisation, %: 25 angina, 25 ischaemia, 21 revascularisation. Diabetes, %: 11 angina, 19 ischaemia, 18 revascularisation.	2 years
Hueb, *et al.*, 1995 (MASS study) Brazil	Patients with stable angina and 1-vessel disease ≥ 80% diameter in LAD and either revascularisation feasible RCT 214 patients	Groups: medical (72) vs. PTCA (72) vs. CABG (70)	Male, %: 82 medical, 81 PTCA, 83 CABG. Mean stenosis, %: 89 medical, 86 PTCA, 88 CABG. Mean age, years: 58 medical, 54 PTCA, 58 CABG. Employed, %: 89 medical, 88 PTCA, 90 CABG. EF, %: 74 medical, 77 PTCA, 74 CABG. Diabetes, %: 20 medical, 15 PTCA, 18 CABG.	2 years (average 3.5 years) Intention-to-treat

Study	Long-term mortality	Angina at follow-up	Long-term MI rate	CABG	Re-PTCA	Conclusions
Pepine, *et al.*, 1994 (for ACIP investigators) USA	4% angina; 2% ischaemia; 0% revascularisation; $p = 0.004$.	Unstable angina: 4% angina; 3% ischaemia; 2% revascularisation.	5% angina; 5% ischaemia; 3% revascularisation (3 PTCA, 1 CABG).	15% angina; 20% ischaemia; 4% revascularisation (7 PTCA, 0 CABG, $p = 0.02$); $p < 0.001$.	9% angina; 7% ischaemia, 5% revascularisation (9 PTCA, 1 CABG, $p = 0.02$).	Pilot data suggest that survival of patients with asymptomatic ischaemia may be prolonged with revascularisation but a larger-scale trial with a longer follow-up needed for confirmation.
Davies, *et al.*, 1997 USA (ACIP 2-year follow-up)	Angina 7%; ischaemia 4%; revascularisation 1%; $p < 0.005$.		Death, MI or recurrent hospitalisation: 42% vs. 39% vs. 23%.	Non-protocol revascularisation: 21% vs. 23% vs. 7%.	Non-protocol revascularisation: 11% vs. 8% vs. 6%.	A strategy of initial revascularisation appears to improve prognosis compared with angina-guided medical therapy but a larger long-term study required to confirm this benefit.
Hueb, *et al.*, 1995 (MASS study) Brazil	0% medical; 1% PTCA; 1% CABG.	Marked suppression of angina: 32% medical; 82% PTCA; 98% CABG; $p < 0.01$ CABG/PTCA and PTCA/medical.	3% medical; 3% PTCA; 1% CABG.	5% medical; 11% PTCA.	4% medical; 29% PTCA; 0% CABG.	The more aggressive approach with initial CABG for patients with a single severe proximal stenosis of LAD artery is associated with lower incidence of medium-term adverse events than PTCA or medical treatment. However, all three strategies resulted in similar incidence of death and infarction during average follow-up of 3 years.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
RITA-II trial participants, 1997 UK and Ireland (multicentre)	PTCA vs. antianginal medical therapy (beta-blockers, calcium antagonists, nitrates, plus aspirin) in patients with significant stenosis in at least one major epicardial vessel 1018 patients	Medical (514) vs. PTCA (504)	Median age, 58 years; women, 18%. Angina grade: none, 20%; 1 or 2, 60%; 3 or 4, 20%. 1-vessel disease 60%; 2-vessel disease 33%; 3-vessel disease 7%.	Average follow-up 2.7 years
Folland, *et al.*, 1997 USA	PTCA vs. medical therapy in clinically stable patients with 1- or 2-vessel disease 328 patients	Patients assigned to PTCA or medical treatment, stratified by number of vessels involved	Baseline characteristics comparable between treatments within all randomisation strata.	Up to 6 years

Study	Long-term mortality	Angina at follow-up	Long-term MI rate	CABG	Re-PTCA	Conclusions
RITA-II trial participants, 1997 UK and Ireland (multicentre)	1.4%; 2.2%	2 years: medical group had 7.6% excess of grade 2+ angina ($p = 0.05$).	Death or MI: 3.3% vs. 6.3%.	5.8% vs. 7.9%.	PTCA or CABG within 1 year in PTCA group: 15.4% vs. 14.9%.	Benefits of PTCA greater in patients with more severe angina at baseline (i.e. higher initial grade of angina and short exercise-time).
Folland, *et al.*, 1997 USA	No difference in MI and death between groups.	2-vessel disease: 67% vs. 47% at 6 months; persisted for up to 4 years of follow-up.				

Health-related quality of life

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Spertus, *et al.,* 1994 USA	HRQoL assessment of series of patients admitted for PTCA surgery and group of medically managed patients with chronic stable angina Prospective series, two centres; 175 patients	Group 1: elective PTCA patients, n = 45. Group 2: medical patients with stable angina, n = 130.	PTCA patients: 84% male, mean age 60 years. Medical patients: 97% male, mean age 69 years.	3 months
Strauss, *et al.,* 1995 (ACME study) USA	HRQoL assessment beside RCT of medical therapy vs. PTCA RCT, multicentre 212 patients	PTCA (105) vs. medical therapy (107) in patients with stable angina, MI in the last 3 months, and > 70% stenosis in proximal two-thirds of one major coronary artery.	Reported elsewhere (Parisi, *et al.,* 1992).	6 months
Spertus, *et al.,* 1995 USA	HRQoL assessment of series of patients admitted for PTCA surgery and group of medically managed patients with chronic stable angina Prospective series, two centres 392 patients (NB: numbers in groups not consistently reported through study)	Group 1: patients undergoing treadmill exercise, n = 70. Group 2: patients with self-reported CAD, n = 84. Group 3: patients with stable angina, n = 160. Group 4: elective PTCA patients, n = 58.	Group 1: 95% male, mean age 61 years. Group 4, n = 45: 87% male mean age 60.2 years.	3 months

Study	Instruments used	Results	Conclusions
Spertus, *et al.,* 1994 USA	RAND SF-36, SAQ (Spertus, *et al.,* 1994)	Results only reported for PTCA patients. SAQ: Baseline mean / 3 month mean / *p* Physical limitation 55.7 / 73.6 / < 0.0001 Angina stability 27.9 / 74.3 / < 0.0001 Angina frequency 46.0 / 79.3 / < 0.0001 Treatment satisfaction 87.8 / 86.3 / 0.6 Disease perception 32.5 / 68.5 / < 0.0001 RAND SF-36: Physical functioning 60.0 / 70.6 / 0.02 General health 59.5 / 58.3 / 0.64 Mental health 63.4 / 68.8 / 0.07 Bodily pain 52.8 / 75.8 / < 0.0001 Role-emotion 46.5 / 65.0 / 0.04 Role-physical 32.0 / 52.3 / 0.003 Social functioning 65.3 / 76.9 / 0.008 Vitality 46.5 / 57.2 / 0.005	Although useful in assessing overall function, a generic health status measure such as the SF-36 may not be responsive enough to detect important clinical changes in a patient's coronary artery disease. Most scales of both questionnaires improved significantly (3 months) after coronary angioplasty.
Strauss, *et al.,* 1995 (ACME study) USA	Exercise duration, angina attack rate, GTN use, MHIQ, PGWB index	Paired data available on 182 patients; paired data on HRQoL and angiograms available on 170 patients. 1. MHIQ — Mean score (SD) / PTCA / Medical Baseline: 96.7 (20.1) / 96.0 (18.6) *p*, NS Change at 6 months: +7.36 (15.6) / +1.98 (14.7) $p = 0.02$ 2. Improved HRQoL noted only in patients demonstrating an increase in exercise time (PTCA and medical) 3. Exercise time and number of angina episodes correlated with physical subscale of HRQoL ($p < 0.001$ for PTCA and medical) but not for PGWB scale. 4. Patients who experienced an improvement in HRQoL were those whose angiograms demonstrated > 18.8% (2 × SD) improvement in lesion severity in both PTCA and medical patients.	Patients randomised to PTCA had significantly greater improvement in overall HRQoL.
Spertus, *et al.,* 1995 USA	RAND SF-36 SAQ (Spertus, *et al.,* 1994)	Results only reported for stable coronary artery disease patients and PTCA patients. SAQ: Stable coronary artery disease n = 13 / Before PTCA n = 45 / After PTCA Physical limitation 50.2 / 56 / 74* Angina stability 52.0 / 28 / 76* Angina frequency 67.5 / 46 / 79* Treatment satisfaction 78.1 / 95 / 93 (NS) Disease perception 56.7 / 32 / 68* * $p < 0.0001$ Correlation of physical limitation scales with exercise treadmill test duration: n / Unadjusted (*p*) / Age-adjusted (*p*) SAQ physical score 70 / 0.36 (0.002) / 0.42 (0.001) SF-36 physical score 26 / 0.29 (0.16) / 0.024 (0.93) CCS class score 70 / 0.14 (0.24) / 0.21 (0.11)	SAQ is a valid and reliable instrument in patients with coronary artery disease.

Cost and cost-effectiveness (model)

Study (per-spective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusions
Kinlay, 1996 Australia (Hospital, government, society)	To examine the cost-effectiveness of PTCA vs. medical therapy in 1-vessel disease.	1.Clinical and economic data pooled to derive cost per successfully treated patient (i.e. freedom from angina) for theoretical cohort of 100 patients with 1-vessel disease (CEA). 2. Sensitivity analysis to test uncertainty.	Clinical: ACME trial. Economic: bottom-up costs from hospital to cost 'average' patient. Rehospitalisation rates from ACME. Resource from ACME and Australian hospitals not clear. (Aus$, 1993/94).	3 years	PTCA minus medical, Aus$: hospital 110,993 government –55,336 patient –11,398 insurance fund 3641 society 47,900 Incremental cost of PTCA over medical, Aus$ (3 years) per additional patient free of angina: 3875.	From viewpoint of hospital, medical strategy saved $110,993 per 100 patients compared with PTCA; however, only 46% of these savings reflected actual savings to society. Most of savings to hospital result from shifting cost of treating patients with 1-vessel disease to government and patient.

Appendix 7

Summary tables of PTCA versus CABG

Clinical effectiveness

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Puel, *et al.*, 1992 France	Patients with multi-vessel disease who are technically eligible for either procedure RCT 109 patients	Groups: CABG (52) vs. PTCA (57)	2-vessel disease: 67% CABG, 88% PTCA. 3-vessel disease: 33% CABG, 12% PTCA. Identical with respect to age, sex, risk factors, symptoms and LVF.	2.8 years
RITA trial participants, 1993 UK	Patients with arteriographically proven coronary artery disease, ≥ 70% reduction in luminal diameter. 3% of 27,975 patients who received an angiogram were randomised RCT, multicentre 1011 patients	Groups: CABG (501) vs. PTCA (510)	Male: 79% CABG, 83% PTCA. Median age: 57 years. 1-vessel disease: 44% CABG, 46% PTCA. 2-vessel disease: 44% CABG, 42% PTCA. 3-vessel disease: 12% CABG, 12% PTCA. No angina: 7% CABG, 7% PTCA. NYHA angina class III or IV: 61% CABG, 57% PTCA.	5 years; mean follow-up 2.5 years Intention-to-treat Dropouts: 11 (2%) CABG, 17 (3%) PTCA
Rodriguez, *et al.*, 1993; 1996 (ERACI) Argentina	Patients > 1- but < 3-vessel disease, amenable to PTCA and CABG, and stenosis ≥ 70% RCT, costs? 127 patients	Groups: CABG (64) vs. PTCA (63)	Male: 89% CABG, 81% PTCA. Mean age, years: 55 CABG, 59 PTCA. 2-vessel disease: 53% CABG, 57% PTCA. 3-vessel disease: 47% CABG, 43% PTCA. EF: 62% CABG, 59% PTCA. Previous MI: 31% CABG, 32% PTCA.	1 year and 3 years Dropouts: 3 (5%) CABG, 1 (2%) PTCA

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	CABG	Re-PTCA	Conclusions
Puel, *et al.*, 1992 France	1 (1.8%) CABG, 0% PTCA.	Total: 7 (12%) CABG, 5 (9.6%) PTCA. 1st year: 2 (2.6%) CABG, 3 (3.9%) PTCA.				Additional reintervention PTCA and/or CABG: 5% CABG, 20% PTCA.		PTCA offers effective alternative to CABG when managing 2-vessel disease. A larger number of patients with 3-vessel disease needed to draw conclusions about this group.
RITA trial participants, 1993 UK	6 (1.2%) CABG, 4 (0.8%) PTCA.	All causes: 18 (3.6%) CABG, 16 (3.1%) PTCA.	6 months: 11% CABG, 32% PTCA, $p < 0.001$. 2 years: 21% CABG, 31% PTCA, $p = 0.007$.		26 (5.2%) CABG, 34 (6.7%) PTCA.	4 (0.8%) CABG, 96 (19%) PTCA. (18%) PTCA.	16 (3.2%) CABG, 93	CABG involves longer hospital stay and convalescence but thereafter surgically treated patients enjoy better relief of angina and require fewer anti-anginal drugs than patients undergoing PTCA.
Rodriguez, *et al.*, 1993; 1996 (ERACI) Argentina	3 (4.6%) CABG, 1 (1.5%) PTCA.	Late deaths: 0% CABG, 2 (3.2%) PTCA. No difference in survival at 1 year; at 3 years: 4.7% vs. 9.5% (NS).	Freedom from angina higher in CABG group. At 3 years: 79% CABG, 57% PTCA, $p < 0.001$.	4 (6.2%) CABG, 4 (6.3%) PTCA.	1 (1.5%) CABG, 2 (3.2%) PTCA; at 3 years: 7.8% vs. 7.8%.	2nd revascular-isation: 3.2% CABG, 32% PTCA. At 3 years need for additional reinterventions: 6% CABG vs. 37% PTCA, $p < 0.001$.		Study found no significant differences in in-hospital major complications between two groups. At 1-year follow-up no differences in survival and freedom from MI; however, patients in CABG group more frequently free from angina and combined events than PTCA group. At 3 years freedom from combined cardiac events was greater in patients initially undergoing CABG. Patients undergoing PTCA had higher incidence of angina recurrence, and need for repeat revascularisation.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Hamm, *et al.*, 1994 (GABI) Germany	Patients aged under 75 years with multi-vessel disease CCS class ≥ 2 and ≥ 70% stenosis, lesions < 2 cm RCT, multicentre 359 patients	Groups: CABG (177) vs. PTCA (182)	Male: 80% CABG, 79% PTCA. 2-vessel disease: 78% CABG, 85% PTCA. 3-vessel disease: 22% CABG, 15% PTCA. Unstable angina: 15% CABG, 13% PTCA. Diabetic: 15% CABG, 10% PTCA.	1 year (3, 6 and 12 month examinations) Dropouts: 16 (9%) CABG, 6 (3%) PTCA
King, *et al.*, 1994 (EAST) USA	Patients with 2- or 3- vessel disease, EF > 25% RCT, multicentre 392 patients	Groups: CABG (194) vs. PTCA (198). Stratum A (113): 2-vessel disease and 1 lesion in each vessel system. Stratum B (123): 2 vessel disease and multiple lesions in ≥ 1 vessel system. Stratum C (51): 3-vessel disease and 1 lesion in each vessel system. Stratum D (105): 3-vessel disease and multiple lesions in ≥ 1 vessel system	Male: 73% CABG, 75% PTCA. 2-vessel disease: 60% CABG, 60% PTCA. 3-vessel disease: 40% CABG, 40% PTCA. Stratum A: 56 (29%) CABG, 57 (29%) PTCA. Stratum B: 61 (31%) CABG, 62 (31%) PTCA. Stratum C: 26 (13%) CABG, 25 (13%) PTCA Stratum D: 51 (26%) CABG, 54 (27%) PTCA. Stenosis ≥ 50%: 74% CABG, 71% PTCA. EF: 62% CABG, 61% PTCA. Diabetes: 21% CABG, 25% PTCA. Hypertension: 52% CABG, 54% PTCA. Angina III or IV: 83% CABG, 77% PTCA.	3 years

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	CABG	Re-PTCA	Conclusions
Hamm, *et al.*, 1994 (GABI) Germany	8 (4.5%) CABG, 2 (1.1%) PTCA (4 CABG and 1 PTCA before procedure).	Total: 9 (5.1%) CABG, 4 (2.2%) PTCA.	Freedom from angina: 74% CABG, 71% PTCA.	13 (7.3%) CABG, 4 (2.2%) PTCA.	Total: 13 (7.3%) CABG, 7 (3.8%) PTCA.	Revascularisation: 44% PTCA, 6% CABG, $p < 0.001$. CABG: 2 (1.1%) CABG, 41 (23%) PTCA.	7 (4%) CABG, 50 (27%) PTCA.	In selected patients with multi-vessel disease, PTCA and CABG as initial treatments resulted in equivalent improvement in angina after 1 year. However, to achieve similar clinical outcomes, patients treated with PTCA were more likely to require further interventions and anti-anginal drugs, whereas patients treated with CABG were more likely to sustain an acute MI at time of procedure.
King, *et al.*, 1994 (EAST) USA	2 (1%) CABG, 2 (1%) PTCA.	12 (6%) CABG, 14 (7%) PTCA.	CCS class > 1: 12% CABG, 20% PTCA, $p = 0.039$.	20 (10%) CABG, 6 (3%) PTCA.	38 (20%) CABG, 29 (14%) PTCA.	1% CABG, 22% PTCA, $p < 0.001$.	CABG 13%, PTCA 41%, $p < 0.001$.	CABG and PTCA did not differ significantly with respect to mortality and rate of MI but there were large differences in the need for revascularisation. Consequently, selection of one procedure over the other should be guided by patients' preferences regarding quality of life and possible need for subsequent procedures.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Goy, *et al.*, 1994 Switzerland	Patients with single, isolated LAD stenosis and no previous coronary intervention. 8% of those with 1-vessel disease (1786) met entry criteria RCT 142 patients	Groups: CABG (LIMA grafts) (66) vs. PTCA (68)	Male: 80% CABG, 80% PTCA. % stenosis before: 79% CABG, 77% PTCA. Minimal lumen diameter before: 0.6 CABG, 0.66 PTCA. Mean age, years: 54 CABG, 57 PTCA. Type A lesion: 46% CABG, 59% PTCA. Type B lesion: 30% CABG, 29% PTCA. Type C lesion: 24% CABG, 12% PTCA. Diabetes: 12% CABG, 12% PTCA. NYHA angina class III or IV: 78% CABG, 80% PTCA.	Median 24 months (12–36) Intention-to-treat One drop-out in CABG group
CABRI trial participants, 1995 Europe	Patients under 76 years, > 1-vessel disease, left ventricular EF > 0.35, > 50% luminal diameter, ≥ 1 vessel suitable for PTCA, ≥ 2 mm diameter RCT, multicentre 1054 patients	Groups: CABG (513) vs. PTCA (541)	Male: 78% CABG, 78% PTCA. Mean age, years: males 59.2 CABG, 59.3 PTCA; females 63.7 CABG, 62.7 PTCA. 2-vessel disease: 56% CABG, 58% PTCA. 3-vessel disease: 43% CABG, 40% PTCA. EF: 0.63 CABG, 063 PTCA. Angina class III or IV: 49% CABG, 45% PTCA. Unstable angina: 15% CABG, 14% PTCA. Diabetes: 12% CABG, 12% PTCA.	1 year (will be followed-up for 10 years) Intention-to-treat
Hueb, *et al.*, 1995 (MASS study) Brazil	Patients with stable angina and 1-vessel disease ≥ 80% diameter in LAD and revascularisation feasible RCT 214 patients	Groups: medical (72) vs. PTCA (72) vs. CABG (70)	Male: 82% medical, 81% PTCA, 83% CABG. Mean stenosis: 89% medical, 86% PTCA, 88% CABG. Mean age, years: 58 medical, 54 PTCA, 58 CABG. Employed: 89% medical, 88% PTCA, 90% CABG. EF: 74% medical, 77% PTCA, 74% CABG. Diabetes: 20% medical, 15% PTCA, 18% CABG.	2 years (average 3.5 years) Intention-to-treat

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	CABG	Re-PTCA	Conclusions
Goy, *et al.*, 1994 Switzerland	None.	Cardiac: 1 (2%) CABG, 0% PTCA. Non-cardiac: 0% CABG, 3 (4.4%) PTCA.	CCS class I: 6-months 95% CABG, 88% PTCA; 1-year 97% CABG, 96% PTCA; 2-year 95% CABG, 94% PTCA.	1 (2%) CABG, 2 (2.9%) PTCA.	Total: 2 (3%) CABG, 8 (12%) PTCA.	0% CABG, 9 (13%) PTCA.	2 (3%) CABG, 8 (12%) PTCA. Total revascularisation, $p < 0.01$.	If restenosis accepted as inevitable event related to PTCA, risk of MI accompanying restenosis and need for reintervention, PTCA remains a simpler initial alternative to CABG. As many important consequences of CABG appear only after 10 years or so, long-term follow-up will probably elucidate more precisely the place of both strategies.
CABRI trial participants, 1995 Europe	9 (1.7%) CABG, 7 (1.3%) PTCA.	Cumulative: 14 (2.7%) CABG, 21 (3.9%) PTCA.	Angina CCS class > 1: 75 (14%) CABG, 52 (10%) PTCA.		18 (3.5%) CABG, 28 (4.9%) PTCA.	15 (2.8%) PTCA group had initial CABG. 4 (0.8%) CABG, 85 (16%) PTCA.	20 (3.9%) CABG group had initial PTCA. 14 (2.7%) CABG, 113 (21%) PTCA.	Risk of reintervention five times greater in PTCA group than CABG group. Findings of this trial consistent with those of previous studies and add to weight of information clinicians need to discuss with patients when options for management of severe angina under consideration.
Hueb, *et al.*, 1995 (MASS study) Brazil		0% medical, 1% PTCA, 1% CABG.	Marked suppression of angina: 32% medical, 82% PTCA, 98% CABG ($p < 0.01$ CABG/PTCA and PTCA/medical).		3% medical, 3% PTCA, 1% CABG.	5% medical, 11% PTCA.	4% medical, 29% PTCA, 0% CABG.	The more aggressive approach with initial CABG for patients with single severe proximal stenosis of LAD artery is associated with lower incidence of medium-term adverse events than PTCA or medical treatment. However, all strategies resulted in a similar incidence of death and MI during an average follow-up of 3 years.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
BARI investigators, 1996; 1997 USA and Canada (Baseline data reported in Rogers, *et al.*, 1995b)	Stable or unstable angina patients, aged 18–80 years, multi-vessel disease suitable for PTCA or CABG, diameter reduction ≥ 50% of ≥ 2 arteries of ≥ 1.5 mm diameter RCT, multicentre 1829 patients	Groups: CABG (914) vs. PTCA (915)	Male: 74% CABG, 73% PTCA. Mean age, years: 61 CABG, 62 PTCA. 3-vessel disease: 41% CABG, 41% PTCA. Black: 7% CABG, 5% PTCA. Diabetes: 25% CABG, 24% PTCA. EF: 58% CABG, 57% PTCA. Stable angina, class III or IV: 16% CABG, 14% PTCA. Unstable angina: 65% CABG, 63% PTCA.	At least 5 years; mean 5.4 years (3.8–6.8 years) Intention-to-treat 2% lost to follow-up
Jones, *et al.*, 1996 USA	Patients undergoing medical therapy, PTCA or CABG between 1984 and 1990 Single-centre prospective cohort 9263 patients	PTCA: 2924 CABG: 3890 Medical therapy: 2449	Few details on baseline characteristics, as these were adjusted for statistically. Patients with ≥ 50% left main stenosis, previous CABG, or 3+ to 4+ mitral regurgitation were excluded.	Up to 10 years, mean of 5.3 years; 97% complete

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	CABG	Re-PTCA	Conclusions
BARI investigators, 1996; 1997 USA and Canada (Baseline data reported in Rogers, *et al.*, 1995b)	12 (1.3%) CABG, 10 (1.1%) PTCA.	111 (12%) CABG, 131 (14%) PTCA. Survival: 89% CABG, 86% PTCA; for diabetes, 81% CABG, 65% PTCA; $p = 0.003$.	5-year: 21% PTCA vs. 15% CABG, $p = 0.007$.	41 (4.6%) CABG, 19 (2.1%) PTCA.	Total: 11.7% CABG, 10.9% PTCA.	1% CABG, 31% PTCA.	7% CABG, 34% PTCA.	Compared with CABG, an initial strategy of PTCA did not significantly compromise 5-year survival in patients with multi-vessel disease, although subsequent revascularisation more often required with this strategy. For treated diabetic patients, 5-year survival significantly better after CABG than after PTCA.
Jones, *et al.*, 1996 USA		PTCA or CABG provided better survival than medicine at all levels of severity. Patients with 1-vessel disease, except those with ≥ 95% proximal LAD stenosis, benefited from PTCA vs. CABG. Patients with 3-vessel disease and those 2-vessel disease patients with ≥ 95% proximal LAD stenosis, benefited from CABG vs. PTCA. All other patients with 2-vessel disease, and those with at least 95% proximal LAD stenosis only, had similar survival with either PTCA or CABG. Benefit greatest for patients with severe 3-vessel disease treated with CABG.						Increasing anatomic disease severity reduces survival in all three treatment groups. Trend favours medicine over CABG, and PTCA over medicine, in least severe disease. In more severe disease, survival favours CABG over medicine or PTCA. Absolute survival advantage of PTCA and CABG increases with CAD severity and is greatest in most severe 3-vessel disease treated with CABG.

Health-related quality of life

Study	Study characteristics	Baseline characteristics	Treatment groups	Instruments used	Follow-up
Papadantonaki, *et al.*, 1994 USA	Prospective cohort comparison 76 patients	CABG 44, PTCA 32. Male: 91% CABG, 78% PTCA. Angina class ≥ III: 61% CABG, 53% PTCA.	Elective PTCA or CABG, age < 70 years; ability to complete questionnaire; freedom from serious chronic illness.	QLI-Cardiac III; POMS; physical functioning; questionnaire developed by Shabelai.	Baseline and 3 weeks after discharge from hospital
Cameron, *et al.*, 1994 Australia	Retrospective comparative series 358 patients	254 PTCA, 104 CABG; no difference between two groups. Mean age, years: 54 PTCA, 55 CABG. Angina class ≥ III: 73% PTCA, 65% CABG.	Consecutive patients undergoing PTCA or CABG for narrowing LAD artery, 1987–89. Exclusions: narrowing < 50%; infarction in right coronary or circumflex arteries requiring revascularisation for evolving acute MI or concomitant surgery for other reasons.	York questionnaire (QALY Toolkit) to provide valuations for disability and distress (Rosser Matrix). Disability measured using 15 questions about daily activities using visual analogue scales.	Median 5.5 years (minimum 2.9, maximum 7.1)
Hlatky, *et al.*, 1995; 1997 USA	HRQoL assessment alongside the BARI RCT 934 patients (sub-set of the BARI trial)	Characteristics similar to all trial patients; majority with 2-vessel disease and preserved LVF (see page 104).	PTCA vs. CABG. As for main BARI trial (see page 104).	Functional status: Duke Activity Status Index (DASI); emotional status: Mental Health Inventory (MHI-5); health perceptions: RAND; single items on social health and cognitive function; self-rated health.	Baseline only
Pocock, *et al.*, 1996 (RITA trial) UK	HRQoL assessment alongside RITA RCT	see page 101.	PTCA vs. CABG (see page 101).	NHP; also reported return-to-work data.	2 years

Study	Results	Conclusions
Papadantonaki, *et al.*, 1994 USA	No difference between two groups at baseline in any of the instruments. Significantly greater improvement between baseline and 3 weeks in PTCA patients compared with CABG patients in mood (POMS) and physical functioning.	Patients undergoing PTCA and CABG have similar mood and physical functioning. Improvement in mood and physical functioning greater after PTCA; may be due to the short follow-up period.
Cameron, *et al.*, 1994 Australia	No significant difference in response to disability questions or Rosser Index (mean (SD): PTCA 0.983 (0.034), CABG 0.987 (0.032)); severe incapacity or disability reported in 9% PTCA and 7% CABG; severe distress in 18% PTCA and 10% CABG.	HRQoL good in both groups.
Hlatky, *et al.*, 1995; 1997 USA	DASI scores showed moderate impairment and significantly correlated with patients' overall health rating and angina status. DASI scores favoured CABG up to 3 years, difference not significant thereafter. MHI-5 score showed better emotional status better preserved with a weaker correlation with health rating and angina. No group differences in emotional health throughout follow-up.	Patients in this sub-study are representative of BARI population as a whole.
Pocock, *et al.*, 1996 (RITA trial) UK	No significant difference in NHP scores between two groups, although patients in CABG group had slightly better scores on all dimensions. NHP scores closely mirrored angina scores. PTCA patients returned to work sooner (40% at 2 months compared with 10% of CABG patients) but this difference had disappeared by 5 months.	Revascularisation greatly improves HRQoL, with similar benefits generated by PTCA and CABG. HRQoL and functional return to work greatly influenced by angina scores.

Cost and cost-effectiveness (primary data)

Study	Design	Baseline characteristics	Selection criteria	Methods
Cohen, *et al.*, 1993 USA	Retrospective sample of hospital accounts. Comparison of standard PTCA (n = 113), stents (n = 64), atherectomy (n = 34) and CABG (n = 89).	Mean age, years: PTCA 59, atherectomy 59, stents 57, CABG 63. Multi-vessel disease: PTCA 38%, atherectomy 21%, stents 38%, CABG 95%.	All patients undergoing, between 1/1/90 and 31/12/91: elective conventional PTCA, directional atherectomy, Palmaz-Schatz stenting with NYA functional class stable angina of single major artery, or SVG, and all elective single and multi-vessel CABG.	Itemised hospital accounts were interrogated to derive charge data. Charges translated into costs using department-specific cost:charge ratios. Catheterisation costs based on actual resource use data; room costs made allowance for intensity of nursing.
Rodriguez, *et al.*, 1993 Argentina and USA	Cost analysis alongside the ERACI RCT.	See page 101 (ERACI study).	See page 101 (ERACI study).	Use of standard unit cost of uncomplicated and complicated PTCA (US$4000 and $5000, respectively), and uncomplicated and complicated CABG ($12,000 and $15,000, respectively).
Sculpher, *et al.*, 1994 UK	Cost analysis alongside the RITA RCT.	See page 101 (RITA study).	See page 101 (RITA study).	Perspective: partial health service. Based on resource use collected in trial: initial and repeat procedures; length of stay in hospitals with different levels of care; anti-anginal medications. Resource use valued using unit costs from two UK centres.
Weintraub, *et al.*, 1995c USA	Cost analysis alongside the EAST RCT.	See page 102 (EAST study).	See page 102 (EAST study).	Perspective: partial health service. Based on hospital charges with some adjustment for cost-to-charge ratios. Includes hospitalisations and procedures but not drug therapy or non-hospital costs. Expressed in 1987 US$.
Kelly, *et al.*, 1985 USA	Comparative prospective single centre cost analysis of cohort of CABG and PTCA patients with 1-vessel disease (not randomised).	Group 1: 51 CABG before PTCA introduction. Group 2: 34 CABG after PTCA introduction. Group 3: 58 successful PTCA. Group 4: 20 unsuccessful PTCA. Male, %: 1 – 80; 2 – 71; 3 – 70; 4 – 79. Mean age, years: 1 – 56; 2 – 56; 3 – 54; 4 – 53.	1-vessel disease.	Perspective: partial health service (hospital), all patients included. Based on hospital charges, includes hospital and clinician fees; excludes outpatient fees. Year or source of costs not reported (US$).

Study	Follow-up	Results	Conclusions
Cohen, *et al.*, 1993 USA	Initial hospitalisation	At 1991 prices, mean (SD) costs per patient: standard PTCA $5396 ($2829), atherectomy $5726 ($2716), stenting $7878 ($3270), CABG $20,937 ($6048).	Key areas of resource use including length of stay were all higher in patients undergoing CABG.
Rodriguez, *et al.*, 1993 Argentina and USA	1 year	By 1-year follow-up, and including subsequent procedures, mean cost per patient of patients randomised to PTCA was $6952, compared with $12,938 in CABG group ($p < 0.01$).	Clear cost difference but small study.
Sculpher, *et al.*, 1994 UK	2 years	Resource use: initial hospital stay longer for CABG patients in ITU, CCU and general wards. More subsequent procedures in patients randomised to PTCA: mean PTCA per patient, 0.231 (PTCA group), 0.028 (CABG group); mean CABG per patient, 0.153 (PTCA group), 0.004 (CABG group). Greater use of anti-anginal medication in PTCA group. Costs (using unit costs from London centre): mean initial costs £3753 (PTCA group), £7319 (CABG group). After 2 years, mean costs £6916 (PTCA group) £8739 (CABG group).	Cost advantage to PTCA declines over period of follow-up.
Weintraub, *et al.*, 1995c USA	3 years	Resource use: 51% PTCA patients required at least one repeat PTCA and/or CABG; 0.5% CABG patients required one or more additional procedures. Costs: mean total hospital costs and professional charges for the initial procedure: $16,223 (PTCA patients), $24,005 (CABG patients), $p < 0.0001$. At 3 years, totals moved closer: $23,734 (PTCA patients), $25,310 (CABG patients), $p < 0.0001$.	Initial costs markedly higher in patients randomised to CABG but differential narrows appreciably by 3 years, although remaining statistically significant.
Kelly, *et al.*, 1985 USA	1 year	Initial length of stay: 1 – 12; 2 – 10; 3 – 5, $p < 0.01$ to other groups; 4 – 20. Days in hospital (average) over 1 year: 1 – 1.4; 2 – 3.8; 3 – 4.3; 4 – 1.5. Mean total hospital charges for 1 year: 1 & 2 – $13,559; 3 & 4 – $7689. No significance tests reported.	Total cost of care per patient 43% lower for PTCA as initial procedure for 1-vessel coronary artery disease. NB: patients not randomised, so groups cannot be compared directly.

continued

Cost and cost-effectiveness (primary data) *contd*

Study	Design	Baseline characteristics	Selection criteria	Methods
Black, *et al.*, 1988 USA	Comparative prospective single centre case-control cost analysis of PTCA vs. CABG in multi-vessel coronary artery disease (not randomised).	Male, %: PTCA 86, CABG 87. Mean age (SD), years: PTCA 56 (11), CABG 58 (9). NYHA angina class III/IV, %: PTCA 35, CABG 48. Previous MI, %: PTCA 43, CABG 42. 3-vessel disease, %: PTCA 14, CABG 26, $p < 0.05$.	100 consecutive PTCA patients with 2-vessel disease, no prior CABG or PTCA. 100 CABG patients matched for age, sex and MI history.	Perspective: partial health service (hospital). Based on costs calculated from hospital charges; includes hospital and clinician fees. Re-revascularisation costs assumed to be same as initial costs. Rehospitalisation data obtained from patient telephone surveys. Excludes pre-procedure costs. Expressed in US$ (year not specified).
Hlatky, *et al.*, 1990 USA	Comparative prospective single centre cost analysis of cohort of PTCA and CABG patients with coronary artery disease (not randomised).	CABG 274; PTCA 115. Other characteristics not reported.	Stable angina, elective procedure within 6 weeks of coronary angiography. No prior CABG, PTCA or MI in previous week: 438 patients from 4574 screened.	Perspective: partial health service (hospital). 438 patients included, complete data for 389. Costs based on four costing methods reported. Method 2 reported here: includes bottom-up resource use and staff costs; units of resource use reported; exclusions not reported. Expressed in US$ (year not specified).
van den Brand, *et al.*, 1990 The Netherlands	Comparative retrospective single centre cost analysis of cohort of PTCA and CABG patients (not randomised). (CABG group: 1971–80; PTCA group: 1980–85)	CABG 1041, PTCA 896. Male, %: PTCA 90, CABG 88. Mean age, years: PTCA 53, CABG 53. > 1-vessel disease, %: CABG 82, PTCA 9. EF < 56%: CABG 31, PTCA 34. Reintervention in year 1, %: CABG 2, PTCA 29.	Admitted for angiography – eligible for CABG or PTCA.	Perspective: partial health service (hospital). Sample of patients included (not clear). Based on hospital costs and charges: includes procedure costs (bottom-up); staff, overheads, depreciation, interest and maintenance costs allocated by 'input-output coefficients'; excludes costs before 1st intervention, rehabilitation costs, unspecified 'medical treatments'. Expressed in 1987 Dutch guilders (Fl) (1 Dfl = 0.49 US$).
Jang, *et al.*, 1984 USA	Comparative prospective multicentre cost analysis of a cohort of CABG and PTCA patients with 1-vessel disease (not randomised).	Group 1: 175 CABG. Group 2: 186 PTCA. Basis for selection of patients from each of 11 centres not specified, % retrieval not reported. Male, %: 1 – 80, 2 – 81. Age range, years: 1 – 34–73, 2 – 33–72.	1-vessel disease.	Perspective: partial health service (hospital), sample of patients included. Based on hospital charges; includes hospital and clinician fees; excludes outpatient fees. Year 1980/81; source of costs not reported (US$).

Study	Follow-up	Results	Conclusions
Black, *et al.*, 1988 USA	1 year	Mean hospital stay (range), days: PTCA 5 (3–25), CABG 13 (7–65). Mean hospital costs, $: PTCA 6185, CABG 15,372. Mean physician fees, $: PTCA 2953, CABG 7398. Mean total initial costs (range), $: PTCA 9138 (4820–33,820), CABG 22,771 (15,601–66,322). Mean 1 year cost, $: PTCA 11,100, CABG 22,862.	CABG more costly at 1 year than PTCA in multi-vessel disease. However, follow-up investigations in PTCA group not costed and would probably have reduced difference. NB: very coarse matching of patients – valid comparison?
Hlatky, *et al.*, 1990 USA	Initial hospital stay only	Mean hospital stay, days: CABG 13.8, PTCA 7.3. ICU, days: CABG 3.1, PTCA 0.5. Blood units: CABG 29.6, PTCA 5.9. Laboratory tests: CABG 86.9, PTCA 27.7. ECG: CABG 7.7, PTCA 4.1. (other resource use units not clear) Mean total costs, $: CABG 9985, PTCA 5392.	Initial hospital costs $4593 less for PTCA but when charges used difference is inflated to $10,087. Thus, use of charges significantly overestimates savings from PTCA.
van den Brand, *et al.*, 1990 The Netherlands	1 year	Procedure costs, US$: PTCA (breakdown included) 3745, CABG (breakdown not included) 4889. Mean 1 year costs with inclusion of re-interventions, US$: CABG 10,468, PTCA 6676, medical (patients who did not undergo either procedure) 2770. NB: sources of procedure or medical treatment costs not reported, probably top-down.	The savings per year highest for medical patients; PTCA patients less costly at 1 year than CABG patients. Ratio, medical:PTCA:CABG, 13:64:100. NB: PTCA patients not concurrent with CABG patients – CABG patients had much more multi-vessel disease: so are groups comparable?
Jang, *et al.*, 1984 USA	Initial admission only	Initial length of stay: 1 – 12 (± 5), 2 – 4 (± 2), $p < 0.001$. Mean total hospital charges, US$: 1 – 15,580 (± 2159), 2 – 5135 (± 2159), $p < 0.0001$.	PTCA for revascularisation in 1-vessel coronary artery disease significantly more effective than CABG in short term.

Cost and cost-effectiveness (model)

Study (per-spective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusions
Wong, *et al.,* 1990	Decision analytical model using data from range of sources. Model compared CABG, PTCA and conservative therapy (no initial revascularis-ation, but this would be undertaken if symptoms continued).	Model incorporated data relating to procedure-related mortality and morbidity, disease-related mortality, benefit from revascularisation, health service costs and HRQoL. US procedure costs were used at 1988 prices. Model was run for range of clinical sub-groups defined in terms of anatomy, symptoms and ventricular function.	Synthesised from various trials and observational studies.	Model run over a sufficiently long period for notional cohort to die.	The results indicated that the most cost-effective form of management depended on relevant clinical sub-group (see page 25 and *Table 4*).	Revascularisation not cost-effective unless symptoms severe or other indications of severe ischaemia or severe multi-vessel disease exist. PTCA may be more cost-effective than CABG when a degree of revascularis-ation similar to that achieved by CABG is feasible and in the elderly with severe co-morbidities.
Wittels, *et al.,* 1990 USA (Third party payer)	To develop a medical cost model to determine the cost of coronary artery disease based on five primary events identified in the Framingham Study (CEA).	Medical decision algorithms developed to show expected therapies and outcomes for acute MI, angina pectoris, unstable angina, sudden death and non-sudden death.	Clinical: data from literature review. Algorithms and probabilities validated by expert panel. Economic data: prices for 70 procedures obtained from Health Care Financing Administration and retail price indices (1986 US$).	5 years after diagnosis (or death, if earlier).	Acute MI: $51,211 Angina pectoris: $24,980 (assuming 40% catheterised, 25% PTCA, 50% CABG, 25% medical). Unstable angina: $40,581 Sudden death/sudden death resuscitated: $9078 Non-sudden death: $13,394 Incorporated effective-ness measures in algorithm, but no increased cost ratios.	Major reason for increased cost of coronary artery disease has been the ability to intervene acutely with new techniques and therapies, such as thrombolytic therapy and CABG surgery.

Appendix 8

Summary tables of non-comparative observational studies relating to CABG only

Clinical effectiveness

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Tyras, *et al.*, 1980 USA	Patients who had isolated CABG to LAD artery Cohort, retrospective 1459 patients	Groups: IMA (765) vs. SVG (694)	Male: 83% IMA, 87% SVG, $p < 0.025$. 1-vessel disease: 8.2% IMA, < 8.8% SVG. Left main stenosis ≥ 50%: 9.3% IMA, 17% SVG, $p < 0.005$. Mean age, years: 52.2 IMA, 53.1 SVG, $p < 0.05$. Normal LVF: 49% IMA, 49% SVG. Unstable angina: 11% IMA, 15% SVG, $p < 0.025$.	Average 44 months; 98% complete follow-up data available
Killen, *et al.*, 1982a; b USA	Patients having at least one isolated CABG Prospective, cohort 2628 patients	CABG	Male: 85%. 2-vessel disease: 32%; age range: 28–78 years. 3-vessel disease: 50%; age range: 50–70 years 69% 1-vessel disease: 17%.	10 years (13,915 patient years, mean 5.3 years per patient)

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Tyras, *et al.*, 1980 USA	1.4% IMA, 1.9% SVG.	5-year survival: 88% IMA, 89% SVG.	Relief same in both groups.	6.6% IMA, 11% SVG, $p < 0.005$.	2.3% IMA, 5.2% SVG, $p < 0.05$.	1974–77: 94% IMA, 90% SVG, $p < 0.01$.	1972–73: 87% IMA, 82% SVG.		IMA grafts to LAD less than 2.5 mm in diameter appear to offer substantial benefits over SVG in terms of graft patency, lower risk of MI and preservation of LVF. The apparent obligatory 'learning curve' remains major obstacle and sequential grafts to 'small' LAD may provide reasonable alternative.
Killen, *et al.*, 1982a; b USA	Total: 26 (1%). 1-vessel disease: 0.4%. 2-vessel disease: 1%. 3-vessel disease: 1%.	Total: 292 (11%). 5-year survival, 90%. 1-vessel disease 95%; 2-vessel disease 91%; 3-vesel disease 89%. Total 10-year survival: 71%.	Free from angina: 81% at 1 year, 57% at 5 years, 37% at 9 years. 1-vessel disease 66%, 2-vessel disease 61%, 3-vessel disease 64% (1 bypass 51%, 4/5 bypass 81%).		3.1 per 100 patient years. 1-vessel disease: 2%; 2-vessel disease: 3% (3/4 bypass 1%); 3-vessel disease: 1/2 bypass 2%; 3 bypass 1%; 4/5 bypass 0.3%.		5% 2nd CABG – 1% per year of follow-up. 1-vessel disease: 1% (1 bypass). 2-vessel disease: 1% (1/2 bypass). 3-vessel disease: 2% (1 bypass), 1% (2/5 bypass).	1 patient had PTCA.	Selected patients can be operated on with low operative mortality and high long-term survival, which for first 5 years approximates to that of 'normal' population. Data also suggest 10 years post-operative survival may approximate to 'normal' in 1- and 2-vessel disease but that patients with 3-vessel disease have deteriorating late course.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Gersh, *et al.*, 1983 (CASS participants) USA	Patients 65 or older who undergoing CABG from CASS registry Prospective, cohort 8744 patients	Groups: age ≥ 65 years (1086) vs. < 65 years (7658)	Male: 74%, age ≥ 65 years. 1-vessel disease: 11% ≥ 65 years. 2-vessel disease: 27% ≥ 65 years. 3-vessel disease: 61% ≥ 65 years, 46% < 65 years, $p < 0.001$. Left main disease: 13% ≥ 65 years; 65–69 years, 74% > 65 years; 70–74 years, 22% ≥ 65 years; 75–84 years, 4% > 65 years. EF < 50%: 22% ≥ 65 years, 22% < 65 years. Diabetes: 15% ≥ 65 years, 11% < 65 years, $p < 0.001$. Angina class III or IV: 72% ≥ 65 years. Unstable angina: 55% ≥ 65 years, 42% < 65 years, $p < 0.001$.	In-hospital only
Laird-Meeter, *et al.*, 1984; 1987a; b The Netherlands	Patients undergoing first CABG for stable or unstable angina despite intensive medication Prospective, cohort. 1041 patients	CABG	Male: 88%. Mean age, years: male 52.6, female 55.2. 1-vessel disease: 19% 2-vessel disease 31%; EF ≥ 55% 58%. 3-vessel disease 42%; EF 31–55% 24%. Left main disease 8%; EF ≥ 30% 2%.	10 years; mean 7.5 years

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Gersh, *et al.*, 1983 (CASS participants) USA	1.9% < 65 years; 5.2% ≥ 65 years, $p < 0.001$.			Procedural: 1.9 per 1000 patients < 65 years; 7.9 per 1000 patients ≥ 65 years; $p < 0.001$.					Despite greater risk of treating elderly patients with CABG, procedure is established and useful therapy that need not be denied to symptomatic elderly patients.
Laird-Meeter, *et al.*, 1984; 1987a; b The Netherlands	Total: 1.2% Male: 1% Female: 2.4%	Total 14%; male 14%; female 13%. 5-year survival: total 92%; 1-vessel disease 97%; 3-vessel disease 90%; normal EF 95%; poor EF 78%. 10-year survival: total 79%; 1-vessel disease 88%; 3-vessel disease 71%; normal EF 86%; poor EF 53%.					89 (8.5%) re-CABG. 10 (1%) both PTCA and re-CABG.	≥ 1 PTCA: 24 (2.3%).	5-year survival after CABG almost as good as in general population but after 5 years mortality increases. Risks are acceptable and medium-term outcome is good as long as procedure is not considered curative.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Sheldon & Loop, 1984 USA	All CABG procedures performed at Cleveland Clinic, Ohio, 1967–82 Retrospective 29,373 patients (32,000 CABG procedures)	CABG – 4659 stable angina patients 1967–75	Male: 89% stable angina. Multi-vessel or left main disease: 1967 67%; 1982 89%; stable angina 81%. Mean age, years: 1967 48.1; 1982 58.4; stable angina 52.2. Grafts per patient: 1967 1.0; 1982 2.9; stable angina 1.8	16 years
Maddern, *et al.*, 1984 Australia	Patients undergoing isolated CABG Multicentre, cohort 4001 patients	CABG	Male: 85% total; 1972 95%; 1981 12%. Mean age, years: 1971 44; 1981 57. Reoperation: 2.1% total Mean number of grafts: 1971 1.3; 1980 3.1.	12 years. 98.8% complete follow-up; 48 patients lost
Barner, *et al.*, 1985 USA	Patients having isolated CABG using IMA Prospective, cohort 1000 patients	CABG using IMA	Male: 86% Mean age, years: men 52.1, women 53.6, $p < 0.025$. Left IMA: 992 grafts. Right IMA 111 grafts. Mean grafts per patient: 1975 1.7; 1983 3.2.	At least 1 year; mean 6.3 years 77 (8%) patients lost to follow-up

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Sheldon & Loop, 1984 USA	8.6% 1967, 1.7% 1975, 1.3% 1982. 1.1% stable. Reoperations: 2.8% 1975, 5.2% 1982.	5-year survival: 89% 1967–70; 92% 1-vessel disease, 87% 2-vessel disease, 88% 3-vessel disease, 85% left main disease, 92% stable. 10-year survival: 77% 1967–70, 82% 1-vessel disease, 76% 2-vessel disease, 65% 3-vessel disease, 74% left main disease.		12% 1967; 4.1% 1975; 0.8% 1982; 3.6% stable. Reoperations: 33% 1967; 4.3% 1975; 5.2% 1982.		Total: 82% 84% 1967–70 86% 1975, 72% 1982.	Re-operations: 1967 4.1%; 1975 3.1%; 1982 8.6%.		Cleveland Clinic mortality declined steadily from 1967. Graft patency rates increased to average of > 80% at 6 or more years post-surgery; 5-year survival rates for patients with stable angina average 92%. Over same period, better non-surgical alternatives have emerged in form of new pharmacological approaches and PTCA. As long as coronary artery disease remains leading cause of death in USA, every effort must be made to find new methods of prevention, controlling progression, and better and more cost-effective treatment.
Maddern, *et al.*, 1984 Australia	Total: 1.4%. 5% 1974, 1% 1980, 1% 1981.	Survival: 1 year 97%; 5 years 91%.	5-years freedom from angina: 93%.	Total 2.6%; 1981 2.4%.					Age of patients, number of grafts and proportion of women rose. Hospital mortality and duration of CABG fell. Poor outcome was obvious within first 12 months. Further review necessary in about 5 years to obtain better picture of long-term outcome for patients undergoing CABG.
Barner, *et al.*, 1985 USA	1-month rate: 1.4%.	Survival: 5 years 93%; 10 years 84%; 12 years 77%.	Recurrence of chest pain: 367 (37%).	37 (3.7%).	Late MI: 75 (7.5%), mean rate/ year 1.5%.	IMA vs. SVG: 1 year: 96% vs. 93%; $p < 0.02$. 5 years: 88% vs. 74%; $p < 0.001$.	Re-operations: 29 (0.85% per year).	6 PTCAs.	Morbidity and mortality for patients having IMA grafting comparable to those for patients having saphenous vein bypass only. Demonstrated superior patency for IMA grafts supports routine use of bilateral IMA grafting.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Richardson & Cyrus, 1986 USA	Patients undergoing elective, primary, isolated CABG Prospective, cohort 1089 patients	Groups: men (833) vs. women (256)	1-vessel disease: 6%. 2-vessel disease: 25%. 3-vessel disease: 55%. Left main stenosis: 14%. Mean age, years: men 55.4, women 59.7, $p = 0.0001$. LVD: 28% men, 26% women. Adult-onset diabetes: 13% men, 24% women, $p = 0.0001$. Mean NYHA class: men 3.1, women 3.3, $p = 0.008$.	5 years
Teoh, *et al.,* 1987 Canada	Patients undergoing isolated CABG Prospective, cohort 1980 patients	Groups: elective (1604), vs. semi-elective (152), vs. urgent (224)	Male: 84% elective, 81% semi-elective, 74% urgent. 1-vessel disease: 6% elective, 5% semi-elective, 11% urgent. 2-vessel disease: 24% elective, 20% semi-elective, 30% urgent. 3-vessel disease: 69% elective, 76% semi-elective, 59% urgent. Mean age, years: 56.7 elective, 57.5 semi-elective, 59.5 urgent. EF > 60%: 52% elective, 48% semi-elective, 47% urgent. EF 40–60%: 28% elective, 26% semi-elective, 29% urgent. EF 20–40%: 17% elective, 24% semi-elective, 20% urgent. EF < 20%: 3% elective, 1% semi-elective, 4% urgent. Reoperation: 2% elective, 2% semi-elective, 8% urgent. NYHA class III or IV:76% elective, 96% semi-elective, 100% urgent.	In-hospital only
Acinapura, *et al.,* 1989 USA	Patients undergoing isolated CABG with graft to LAD Multicentre, prospective, cohort 3853 patients	Groups: IMA (2100) vs. SVG (1753)	Male: 68% IMA, 66% SVG. Left main disease: 19% IMA, 21% SVG. Mean age, years: 62.3 IMA, 64.7 SVG, $p < 0.01$. EF < 45%: 51% IMA, 48% SVG. Diabetes: 18% IMA, 21% SVG.	9 years maximum 6121 patient years

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Richardson & Cyrus, 1986 USA	1.2% men, 4.3% women, $p = 0.001$.	5-year survival: 91% men, 82% women.		Total: 2.1%. 2.4% men, 1.2% women.					Despite disparity of results between men and women, the authors recommend CABG for women with significant angina, multi-vessel disease and overall reasonably good health, but recommend caution in small women with high-risk of peri-operative MI, respiratory failure and increased operative mortality.
Teoh, *et al.,* 1987 Canada	EF > 60%: 1.5%. EF 40–60%: 3.1%. EF 20–40%: 8.2%. EF < 20%: 17%. NYHA III: 2.7%. NYHA IV: 5.7%. Elective: 2.9%; Semi-elective: 3.9%; Urgent: 8.5%. Male 2.7%; female 7.4%. Reoperation: 3.4%. No re-operation: 6.7%.		EF > 60%: 7.4. EF 40–60%: 8.4%. EF 20–40%: 12%. EF < 20%: 11%. NYHA III: 7.5%. NYHA IV: 4.3%. Elective: 8.1%; semi-elective: 12%; urgent: 12%.					Patients with unstable angina requiring urgent revascularisation face increased risk of operation. Preoperative preparation and improved myocardial protection may reduce the extent of perioperative ischaemia and improve results in these patients.
Acinapura, *et al.,* 1989 USA	1.6% IMA, 1.7% SVG.	10% IMA, 22% SVG, $p < 0.01$.	18% IMA, 31% SVG, $p < 0.01$.	2% IMA, 2.2% SVG.			0.5% IMA, 6.2% SVG, $p < 0.005$.		Patients receiving *in-situ* IMA grafts to LAD have improved long-term survival, fewer recurrent symptoms and fewer late cardiac-related events.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
MacManus, *et al.*, 1990 USA	Patients undergoing primary, isolated CABG Prospective, cohort 4697 patients	CABG	Male: 74%.	In-hospital only
Morris, *et al.*, 1990 USA	Patients undergoing CABG for stable, unstable or progressive angina or acute evolving MI Prospective 1063 patients	Groups: single (420) vs. multiple IMA graft (643)	Mean age, years: 60 single, 60 multiple IMA. Aged ≥ 65 years: 33% single, 34% multiple IMA. Mean EF: 51% single, 49% multiple IMA. EF < 40%: 26% single, 26% multiple IMA. Unstable angina: 41% single, 43% multiple IMA. Acute MI: 6% single, 5% multiple IMA. Elective surgery: 53% single, 52% multiple IMA.	4 years

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
MacManus, *et al.*, 1990 USA	Diabetes: 5.3%. Unstable: 5.6%. Prior MI: 3.6%. Aged > 70 years: 8.4%. EF < 40%: 4%. Female: 6%. (All $p < 0.001$) Hypertension: 3.4%, $p < 0.05$.								Barring a dramatic, unforeseen breakthrough in management of patients with coronary artery disease, the authors expect slowly increasing mortality associated with CABG. Earlier studies comparing medical and surgical therapy must be reconsidered in the light of changing surgical population. Additionally, stratification by risk factors in analysing CABG mortality will become more critical.
Morris, *et al.*, 1990 USA	30-day survival total: 97% single IMA, 98% multiple. Age < 65 yrs: 98% single IMA, 99% multiple. Age ≥ 65 yrs: 93% single IMA, 97% multiple. EF ≥ 40%: 97% single IMA, 99% multiple. EF < 40%: 95% single IMA, 96% multiple. Diabetes: 92% single IMA, 97% multiple. Non-diabetes: 98% single IMA, 98% multiple.	4-year survival total: 93% single IMA, 90% multiple. Age < 65 years: 97% single IMA, 93% multiple. Age ≥ 65 years: 84% single IMA, 89% multiple. EF ≥ 40%: 95% single IMA, 94% multiple. EF < 40%: 87% single IMA, 82% multiple. Diabetes: 88% single IMA, 87% multiple. Non-diabetes: 94% single IMA, 91% multiple.				Re-operation: 0.9% single IMA, 0.9% multiple.			With an average of 4 years follow-up, routine use of multiple IMA grafts seems to provide little additional clinical benefit over routine single IMA in the spectrum of patients undergoing revascularisation. At present, single IMA grafting with adjunctive use of vein grafts may be successfully applied to 90% of patients, offers excellent long-term results, may be associated with less perioperative morbidity than multiple IMA grafting and should be considered the routine standard of current practice.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Salomon, *et al.,* 1990 USA	Patients having initial CABG or reoperation Prospective, cohort 7059 patients	Groups: Initial CABG (6591) vs. reoperation (508)	Male: 79% initial CABG, 82% reoperation. Mean age, years: 59.8 initial CABG, 59.8 reoperation (55.2 at 1st operation), $p < 0.05$. EF: 63% initial CABG, 61% reoperation. Insulin diabetes: 5% initial CABG, 6% reoperation. Angina class II: 4% initial CABG, 3% reoperation. Angina class III: 47% initial CABG, 48% reoperation. Angina class IV: 44% initial CABG, 46% reoperation. Mean number grafts/patient: 2.85 initial CABG, 2.42 reoperation, $p < 0.05$.	Maximum 18 years
Azariades, *et al.,* 1990 USA	Patients over 70-years-old undergoing isolated CABG Prospective, cohort 1081 patients	Groups: IMA graft (354) vs. non-IMA graft (727)	Male: 69% IMA, 67% non-IMA. 1-vessel disease: 7% IMA, 9% non-IMA. 2-vessel disease: 17% IMA, 18% non-IMA. 3-vessel disease: 40% IMA, 36% non-IMA. ≥ 4-vessel disease: 36% IMA, 37% non-IMA, $p = 0.04$. Mean age, years: 74.1 IMA, 75.4 non-IMA. Normal LVF: 44% IMA, 37% non-IMA, $p = 0.1$. Previous CABG: 3% IMA, 4% non-IMA. Diabetes: 17% IMA, 18% non-IMA. Stable angina: 55% IMA, 45% non-IMA. Unstable angina: 7% IMA, 9% non-IMA.	5 years IMA group 93% complete follow-up, non-IMA group 90% complete

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Salomon, *et al.,* 1990 USA	Total: 2% initial CABG, 6.9% re-operation, $p < 0.001$. Elective: 1.8% initial CABG, 6.3% re-operation. Emergency: 6.9% initial CABG, 23% reoperation. Age, years, initial CABG: < 70, 1.4%; > 70, 4.8%. Male:female, initial CABG: 1.8%:3.7% EF < 60%: 2.7% initial CABG, 7% re-operation. EF > 60%: 1.3% initial CABG, 3.5% re-operation.	5-year survival: 89% initial CABG, 81% reoperation. 10-year survival: 74% initial CABG, 65% re-operation, $p < 0.001$.					Probability of re-operation after initial CABG: 3.4% at 5 years and 5.5% at 10 years.		Heart-related event-free status for reoperation group consistently inferior to that of initial CABG group. 10 years after repeat CABG, only 30% of patients free from cardiac symptoms, whereas 50% of patients having single operation asymptomatic.
Azariades, *et al.,* 1990 USA	2.8% IMA, 7.6% non-IMA, $p = 0.003$.	5-year survival: 89% IMA, 78% non IMA.	NYHA I: 73% IMA, 67% non-IMA. NYHA II: 14% IMA, 17% non-IMA.	1.4% IMA, 1.9% non-IMA.	Freedom from MI: 98% IMA, 97% non-IMA.		Freedom from re-operation: 99% IMA, 99% non-IMA.		Patient selection factors clearly shown to play important role in different results between IMA and non-IMA patients older than 70 years. As in younger patients excellent results can be achieved in elderly patients undergoing CABG.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Stahle, *et al.*, 1991 Sweden	Patients with stable angina who had elective CABG Cohort, retrospective 2659 patients	CABG	Male: 86%. Mean age, years: < 40, 4%; 41–50, 15%; 51–60, 45%; 61–70, 33%; > 70, 3%. Reoperation: 2%. Diabetes: 2%. Hypertension: 11%. NYHA class III: 96%. NYHA class IV: 1%.	In-hospital only
Acinapura, *et al.*, 1992 USA	Patients with CABG to anterior descending artery Multicentre, cohort 7470 patients	Groups: IMA grafts (5125) vs. SVG (2345)	Male: 68% IMA, 66% SVG. Mean age, years: 66 IMA, 66 SVG. Left main stenosis: 20% IMA, 21% SVG. EF < 40%: 68% IMA, 65% SVG.	Mean 8.5 years (range 6 months–13 years)
King, *et al.*, 1992a USA	Women who had a first CABG, and age-matched group of men picked at random from all those who had first CABG Retrospective 930 patients	Groups: women (465) vs. age-matched men (465)	Left main stenosis: 16% women, 18% men. Mean age, years: 64.2. White: 97% Married: 57% women, 88% men, $p < 0.001$. Diabetes: 23% women, 13% men, $p < 0.001$. Post-MI angina: 15% women, 7% men, $p < 0.001$. History of smoking: 54% women, 74% men, $p < 0.001$.	In-hospital only

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Stahle, Sweden *et al.*, 1991	Total: 2.6%; male: 2.3%. Age, years: 61–70, 3.4%; > 70, 7.6%. Reoperation: 3.4%. Diabetes: 4.3%. NYHA III: 2.5%. NYHA IV: 13%.								It was not possible to identify high-risk groups in this study. In patients operated on for stable angina, these risk factors identified revealed only moderately high risks. In the clinical situation they are outweighed by unknown factors or factors difficult to assess, such as surgical and anaesthesiological methods and the quality of postoperative care.
Acinapura, *et al.*, 1992 USA	1.8% IMA, 2.4% SVG.	20% IMA, 30% SVG, $p < 0.01$.	Recurrent angina: 15% IMA, 31% SVG, $p < 0.01$.	2% IMA, 2.2% SVG.		96% IMA, 70% SVG, $p < 0.05$.	Re-operation or PTCA: 1.2% IMA, 10% SVG, $p < 0.05$.		Patients who receive *'in-situ'* IMA grafts to LAD coronary artery have improved long-term survival, and fewer recurrent symptoms and late cardiac events. Patients with recurrent angina are more likely to be managed medically, probably as a result of improved long-term patency of IMA.
King, *et al.*, 1992a USA	4.3% women, 3.7% men.		1.3% women, 0.4% men.	Peri-operative: 6.7% women, 4.9% men. Post-operative: 2.6% women, 1.7% men.					No difference in mortality found between men and women matched for age in the current series. Factors previously hypothesised to place women at greater risk, such as higher incidences of hypertension, diabetes and congestive heart failure, not related to mortality for women in this study.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Liao, *et al.*, 1992 USA	Black patients who underwent isolated CABG for coronary artery disease Retrospective, cohort 1719 patients	Groups: men (780) vs. women (939)	1-vessel disease: 26% men, 34% women. 2-vessel disease: 29% men, 26% women. 3-vessel disease: 44% men, 40% women. Left main disease: 8% men, 7% women. Mean age, years: 55.8 men, 58.2 women, $p < 0.01$. Mean EF: 57% men, 65% women, $p < 0.01$. Diabetes: 22% men, 33% women, $p < 0.01$. Angina: 51% men, 58% women, $p < 0.05$.	4 years
Christakis, *et al.*, 1992 Canada	Patients with isolated CABG Multicentre, cohort 12,471 patients	Groups: left ventricular EF > 40%, 9445; left ventricular EF 20–40%, 2539; left ventricular EF < 20%, 487	Left ventricular EF: > 40% / 20–40% / < 20% Male, %: 80 / 85 / 85 ($p < 0.0001$) Left main disease, %: 15 / 15 / 20 ($p < 0.0001$) 1-vessel disease, %: 8 / 2 / 2 2-vessel disease, %: 24 / 21 / 22 3-vessel disease, %: 68 / 77 / 76 ($p < 0.0001$) Age ≥ 40 years, %: 3 / 3 / 2 Age 40–49 years, %: 14 / 12 / 13 Age 50–59 years, %: 35 / 32 / 33 Age 60–69 years, %: 37 / 38 / 37 Age ≥ 70 years, %: 11 / 15 / 15 ($p < 0.0001$) Reoperation, %: 4 / 7 / 5 Stable angina, %: 81 / 77 / 71 ($p < 0.0001$) IMA graft, %: 48 / 42 / 31 ($p < 0.0001$)	In-hospital only
Bell, *et al.*, 1992 USA	Patients from CASS registry with 3-vessel disease who had CABG Multicentre, cohort 3372 patients	Groups: angina CCS class I or II, 894; angina CCS class III or IV, 2478	1-vessel bypass, 67 (2%); 2-vessel bypass, 1065 (32%); 3-vessel bypass, 1276 (38%); > 3-vessel bypass, 964 (29%). 1-vessel bypass / 2-vessel bypass / 3-vessel bypass / > 3-vessel bypass Male, %: 87 / 86 / 86 / 89 Age, years: 54 / 56 / 56 / 57 Proximal vessel involvement: None: 13 / 12 / 9 / 11 1: 22 / 27 / 27 / 25 2: 27 / 29 / 38 / 36 3: 37 / 32 / 26 / 27 ($p \geq 0.0001$) EF, %: 56 / 57 / 59 / 58 ($p = 0.043$) ≥ 1 associated disease, %: 43 / 57 / 56 / 57	Mean 4.9 years

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Liao, *et al.*, 1992 USA		4-year survival: 83% women; 75% men; $p = 0.02$.							Demonstrates that, in black patients, gender is not an important independent predictor of cardiac and all-cause mortality for those with sufficient coronary artery disease.
Christakis, *et al.*, 1992 Canada	2.3% > 40%; 4.8% 20–40%; 9.8% < 20%; $p < 0.001$.			6% > 40%; 8% 20–40%; 11% < 20% ($p < 0.0001$).					Most important preoperative intervention may be careful selection of patients for operation. Best candidates for revascularisation are patients with good distal vessels or viable but nonfunctioning myocardium.
Bell, *et al.*, 1992 USA	1.8% CCS class I/II; 3.5% CCS class III/IV.	Adjusted 6-year survival: 1 graft, 85% CCS class I/II; 78% CCS class III/IV. 2 grafts, 89% CCS class I/II; 81% CCS class III/IV. 3 grafts, 92% CCS class I/II; 86% CCS class III/IV. > 3 grafts, 88% CCS class I/II; 86% CCS class III/IV.	> 1 graft more likely to be free from angina than 1 graft.		529 (16%).				Findings do not suggest that complete revascularisation should be attempted in patients in whom it can be achieved but emphasise that bypassing the three major coronary arteries is particularly necessary in patients with severe ischaemia and LVD.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics				Follow-up
Rahimtoola, *et al.*, 1993a USA	Patients with isolated CABG for angina Prospective, cohort 7529 patients	Early cohort (1969–73) 503; late cohort (1973–88) 7026		Total	early	late	20 years
			Male, %:	78	85	78 ($p < 0.0001$)	
			1-vessel disease:	13	21	12	
			2-vessel disease:	22	37	21 ($p < 0.0001$)	
			≥ 3-vessel disease:	53	35	55	
			Mean age, years:	60.7	53.7	61.1 ($p < 0.0001$)	
			Normal LVF, %:	47	45	47	
			Prior CABG, %:	3	1	3 ($p < 0.05$)	
			Diabetes, %:	12	9	13 ($p < 0.01$)	
			Hypertension, %:	42	24	44 ($p < 0.0001$)	
			Current smoker, %:	30	44	29 ($p < 0.0001$)	
			Stable angina, %:	74	83	74 ($p < 0.0001$)	
			1 graft, %:	15	40	14	
			2 grafts, %:	31	45	30 ($p < 0.0001$)	
			≥ 3 grafts, %:	54	16	56	
Christakis, *et al.*, 1993 Canada	Patients undergoing isolated CABG Prospective, cohort 1228 patients	Groups: CABG only, 911; TEA with CABG, 317	Male: 88% TEA, 83% CABG, $p = 0.04$. 1-vessel disease: 3.8% TEA, 8.5% CABG. 2-vessel disease: 15% TEA, 28% CABG. 3-vessel disease: 81% TEA, 63% CABG, $p < 0.001$. Age < 40 years: 1.9% TEA, 1.5% CABG. Age 40–59 years: 47% TEA, 45% CABG. Age 60–69 years: 34% TEA, 41% CABG. Age > 69 years: 17% TEA, 12% CABG, $p = 0.06$. EF > 60%: 48% TEA, 54% CABG. EF 40–59%: 34% TEA, 28% CABG. EF 20–39%: 15% TEA, 16% CABG. EF < 20%: 2% TEA, 2.2% CABG. NYHA class III or IV: 64% TEA, 71% CABG. Stable angina: 33% TEA, 26% CABG. ≥ 3 bypasses: 83% TEA, 71% CABG.				5 years, mean 4.2 years. 97% complete follow-up; 8 patients lost

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Rahimtoola, *et al.*, 1993a USA	Total, 2.4%; early, 7%; late, 2.1%; $p < 0.0001$.	Mortality/year: 1–10 years, 2.7%; 11–20 years, 3.5%. Total 20-year survival: 38%. 15-year survival: early 47%; late 55%; $p < 0.0001$.	NHYA class I: 60% men, 48% women. class II: 21% men, 26% women. class III: 13% men, 19% women. class IV: 5% men, 8% women. $p < 0.001$.		Incidence: 10 years 16%, 15 years 26% (men and women). Rate/year: 1.2% 1–5 years, 2% 6–10 years, 2% 11–15 years.		10 years: 16% men, 18% women; 15 years: 34% men, 31% women; $p = 0.1$. Rate/year: 0.6% 1–5 years, 2.5% 6–10 years, 3.5% 11–15 years.		Results of CABG up to 20 years later better than predictions based on earlier studies. Although women experienced statistically significant higher operative mortality rate, lower long-term survival and less relief of angina than men, differences were small and probably not clinically meaningful. Thus, use of CABG in women should not be denied or restricted provided usual indications for surgery are present.
Christakis, *et al.*, 1993 Canada	3.2% TEA, 3.8% CABG.	TEA 5-year survival: 90%.	66% TEA free from angina.	6% TEA, 5.5% CABG.	TEA new MI in follow-up: 5.4%.				Demonstrates that TEA did not increase risk of operative mortality compared with CABG. Long-term results were comparable. TEA can thus be performed with safety and efficacy when strict guidelines for its use are followed.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Rahimtoola, *et al.*, 1993b USA	Patients undergoing CABG for unstable or chronic stable angina Prospective, cohort 8906 patients	Groups: men (6927) vs. women (1979)	1-vessel disease: 14% men, 19% women. 2-vessel disease: 19% men, 21% women. ≥ 3-vessel disease: 54% men, 50% women, $p < 0.0001$. Left main disease: 13% men, 10% women. Mean age, years: 61 men, 64 women, $p < 0.0001$. Abnormal LVF: 52% men, 45% women, $p < 0.0001$. Prior CABG: 12% men, 9% women, $p < 0.0001$. Diabetes: 12% men, 22% women, $p < 0.0001$. Unstable angina: 30% men, 34% women, $p < 0.0001$.	15–18 years; 89% complete follow-up
Mantia, *et al.*, 1994 USA	Patients who had elective CABG in four non-university hospitals Multicentre, cohort 1095 patients	CABG	None.	In-hospital only

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Rahimtoola, *et al.*, 1993b USA	Total: 1.9% men, 2.7% women, $p = 0.02$. ≥ 3 vessel disease: 2% men, 3.8% women. Abnormal LVF: 2.6% men, 4.1% women, $p = 0.04$. Age 55–64 years: 1.7% men, 2.8% women, $p = 0.05$. Stable: 1.5% men, 2.6% women, $p = 0.006$.	Survival: 5 years, 88% men, 86% women; 10 years 73% men, 70% women; 15 years 54% men, 50% women; 18 years 42% men, 37% women; $p = 0.03$. Stable angina: 5 years 88% men, 85% women; 10 years 73% men, 69% women; 15 years 54% men, 47% women; $p = 0.005$.	Class I: 58% men, 47% women. Class II: 20% men, 23% women. Class III: 15% men, 18% women. Class IV: 7% men, 12% women. ($p < 0.0001$)		5 years: 6% men, 7% women. 10 years: 16% men, 15% women. 15 years: 28% men, 26% women.		5 years: 3% men, 4% women. 10 years: 15% men, 16% women. 15 years: 32% men, 30% women.		Women have higher operative mortality and lower long-term survival than men after CABG for angina. However, differences are small, even if statistically significant. Importantly, patient-related factors (not gender) are independent predictors of poorer survival. Thus, CABG should not be delayed or denied to women with usual indications for surgery.
Mantia, *et al.*, 1994 USA	Total: 45 (4.1%).	Highly predictive factors of mortality: unstable angina or recent MI; evidence of chronic heart failure at time of surgery. Age > 65 years.							Results same as for university hospitals. Data collected simultaneously at both university and non-university hospitals would allow valid comparisons of both risk factors and outcome as they relate to mortality.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Schmuziger, *et al.*, 1994 Switzerland	Patients undergoing CABG for first time or reoperation Multicentre, prospective, cohort 3103 patients	Groups: first CABG (2645) vs. reoperation (458)	Male: 83% 1st CABG, 85% reoperation. 1-vessel disease: 4% 1st CABG, 3% reoperation. Multi-vessel disease: 96% 1st CABG, 97% reoperation. Left main stenosis: 28% 1st CABG, 23% reoperation, $p < 0.05$. Mean age, years: 61 1st CABG, 60 reoperation. Age > 65 years: 29% 1st CABG, 26% reoperation. Mean EF: 60% 1st CABG, 56% reoperation. Diabetes: 9% 1st CABG, 12% reoperation. NYHA class I/II: 44% 1st CABG, 33% reoperation, $p < 0.001$. NYHA class III: 51% 1st CABG, 9% reoperation, $p < 0.001$. NYHA class IV: 5% 1st CABG, 58% reoperation, $p < 0.001$. Unstable angina: 29% 1st CABG, 40% reoperation, $p < 0.001$.	Mean 16.5 months; reoperations only followed-up (81% complete data)

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Schmuziger, *et al.*, 1994 Switzerland	2.3% 1st CABG, 9.2% reoperation, $p < 0.001$. Elective: 2% 1st CABG, 8.6% re-operation. Emergency: 35% 1st CABG, 29% reoperation. Age < 65 yrs: 1.8% 1st CABG, 7.4% reoperation. Age > 65 yrs: 4% 1st CABG, 14% re-operation. NYHA class I/II: 0.8% 1st CABG, 3% reoperation. class III/IV: 4% 1st CABG, 12% reoperation. EF > 40%: 1% 1st CABG, 8% reoperation. EF < 40%: 9% 1st CABG, 16% reoperation. Left main disease: 2% 1st CABG, 16% reoperation. No left main disease: 2% 1st CABG, 7% reoperation.	Reoperation: 6 (1.8%).	Re-operation NYHA class I–II: 93%. NYHA class III–IV: 7%.	1.3% 1st CABG, 2.2% reoperation.					From present experience reoperative CABG is effective but causes an increase in operative mortality, especially in patients identified as NYHA class III or IV, with unstable angina, left main stem stenosis and poor LVF. Late survival is excellent; most patients will be free of cardiac events and in good condition clinically for at least 5 years.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Cameron, *et al.*, 1995 USA	Patients from CASS registry who had first CABG to single site Retrospective, cohort 9557 patients (Registry 24,958 patients)	CABG: predictive group used to develop model (5289). Angina (4036) vs. no angina (1253) at follow-up	Male: 84% no angina, 81% angina, $p = 0.03$. Minimal coronary disease: 0.75% no angina, 1.8% angina, $p = 0.001$. Mean age, years: 54.9 no angina, 53.9 angina, $p < 0.001$. Diabetes: 11% no angina, 12% angina. Preoperative angina: 92% no angina, 96% angina, $p < 0.001$. Complete revascularisation: 74% no angina, 70% angina, $p = 0.003$. Vein grafts only: 84% no angina, 80% angina, $p = 0.001$.	4–8 years
Risum, *et al.*, 1995 Norway	Patients with isolated CABG for angina Prospective, cohort 1025 patients	CABG	Male: 89%. NYHA class III: 69%; class IV: 22%. 1-vessel disease, 8.6%; 2-vessel disease, 24%; 3-vessel disease, 66%. Unstable angina: 19%. Previous PTCA, 2.5%; previous heart surgery, 2.2%. Diabetes: 4.4%. IMA bypass: none – 4.5%; 1 – 12%; 2 – 32%; 3 – 34%; ≥ 4 – 17%.	Median 6.5 years

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Cameron, *et al.*, 1995 USA			Year 1: 1253 (24%). Year 6: > 40%. 1-vessel disease: 25%. 2-vessel disease: 24%. 3-vessel disease: 22%.		Probability of MI higher in those with angina at 1 year than in those without angina ($p = 0.04$).		Rate of reoperation higher in those with angina at 1 year than in those without ($p = 0.003$).		Predictors of postoperative angina are: preoperative angina, previous MI, younger age, female gender, hypertension diabetes, incomplete revascularisation and use of vein grafts only. Adverse clinical implications of postoperative angina, namely increased risk of MI and need for reoperation, mandate further clinical evaluation of patients with postoperative angina.
Risum, *et al.*, 1995 Norway	Total: 3%. 1-vessel disease: 2.3%. 2-vessel disease: 1.2%. 3-vessel disease: 3.7%. Left main disease: 6.1%, $p = 0.004$. NYHA class III, 2.2%; class IV, 5.7%; $p = 0.03$. Diabetes: 2.2%. Unstable: 6.2%, $p = 0.005$.	1-year survival: 95%. 5-year survival: 89%. 9-year survival: 84%.							Risk factors for early mortality (absence of sinus rhythm, previous heart surgery, mitral valve regurgitation, left main stenosis and unstable angina) are good indicators for the outcome of CABG, identifying all deaths; however, long-term mortality cannot be predicted.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Brandup-Wognsen, *et al.*, 1995 Sweden	CABG patients without concomitant procedures or reoperations Multicentre, prospective, cohort 2000 patients	CABG	Male: 81%. Median age (range), years: 64 (32–86). Age: ≥ 50 years, 11%; 51–60 years, 25%; 61–70 years, 45%; ≥ 70 years 19%. 1-vessel disease, 7%; 2-vessel disease, 27%; 3-vessel disease, 66%. Left main disease: 20%. NYHA class I, 3%; class II, 12%; class III, 58%; class IV, 27%. EF < 60%: 35%. Previous PTCA: 5%. Diabetes: 12%. Hypertension: 37%. Smoker: 13%.	2 years
Weintraub, *et al.*, 1995a USA	Patients undergoing first CABG reoperation Prospective, cohort 2030 patients	Groups aged < 50 years (244), 50–59 years (629), 60–69 years (779), ≥ 70 years (381)	Age group, years: < 50 / 50–59 / 60–69 / > 70 Male, %: 86 / 87 / 83 / 79 (p = 0.009) 1-vessel disease, %: 9 / 7 / 5 / 5 2-vessel disease, %: 25 / 24 / 20 / 17 3-vessel disease, %: 51 / 53 / 52 / 57 (p = 0.004) Left main disease, %: 14 / 16 / 23 / 21 Mean EF, %: 52 / 52 / 51 / 50 EF < 50%, %: 36 / 36 / 43 / 43 Diabetes, %: 16 / 20 / 25 / 23 Angina class III or IV, %: 71 / 75 / 78 / 78 Mean age: 61 years	Mean 4.3 years; 99% complete follow-up

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Brandup-Wognsen, *et al.*, 1995 Sweden	Female, 6%; male, 2.3%; p < 0.001. Age ≤ 50 yrs, 2.3%; age > 70 yrs, 4.8%; p < 0.01. EF: < 40%, 4.1%; ≥ 60%, 2%; p < 0.05. 1-vessel disease, 2%; 3-vessel disease, 4.1%; p < 0.01. Left main disease, 5.1%; no left main disease, 2.5%; p < 0.01.	Female, 6%; male, 3.8%. Age ≤ 50 years, 1.9%; age > 70 years, 6.1%; p < 0.001. EF: < 40%, 7.9%; ≥ 60%, 3.6%; p < 0.05. 1-vessel disease, 1.4%; 3-vessel disease, 4.5%. Left main disease, 5.2%; no left main disease, 4%.							With exception of renal dysfunction, preoperative risk factors for deaths within 30 days after CABG differ from risk factors for deaths between 30 days and 2 years after CABG.
Weintraub, *et al.*, 1995a USA	Total: 7%; < 50 years, 6%; 50–59 years, 4%; 60–69, 8%; ≥ 70 years, 10%; p < 0.0001.	5-year survival: 76%. 10-year survival: 55%.	Total: 41%. < 50 years, 51%; 50–59 years, 48%; 60–69 years, 39%; ≥ 70 years, 26%; p = 0.0001.	Total: 6%. < 50 years, 8%; 50–59 years, 6%; 60–69 years, 5%; ≥ 70 years, 5%.	5-year freedom from MI and alive: 63%. 10-year freedom from MI and alive: 40%.		5-year freedom from CABG: 96%. 10-year freedom from CABG: 76%.	5-year freedom from PTCA: 90%. 10-year freedom from PTCA: 73%.	The constancy of in-hospital results despite older and more severely diseased population in recent years suggests gradually improving techniques. There was a continuing incidence of MI after hospital discharge as well as additional revascularisation procedures. There is no substitute for good comparative studies to assess which patients need additional revascularisation and which overlapping patients are suited for either catheter-based or surgical procedures.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Mickleborough, *et al.*, 1995 Canada	Patients undergoing isolated CABG Prospective, cohort 1487 patients	Groups: men (1132) vs. women (355)	1-vessel disease: 6.6% men, 12% women, $p < 0.001$. 2-vessel disease: 27% men, 32% women. 3-vessel disease: 52% men, 47% women. Left main stenosis: 15% men, 10% women, $p < 0.001$. Mean age, years: 58.6 men, 61.9 women. Mean EF: 47% men, 51% women, $p < 0.001$. EF > 60%: 36% men, 47% women, $p < 0.001$. Diabetes: 18% men, 27% women, $p < 0.001$. CCS class III or IV: 72% men, 83% women, $p < 0.001$. Unstable angina: 18% men, 21% women.	In-hospital only
Jaglal, *et al.*, 1995 Canada	Patients with isolated CABG Multicentre, cohort 5175 patients	Groups: men (4059) vs. women (1116)	Multi-vessel disease: 76% men, 75% women. Limited disease: 9.1% men, 11% women. Left main stenosis > 50%: 14% men, 13% women. Age < 60 years: 42% men, 28% women. Age 60–69 years: 39% men, 43% women. Aged ≥ 70 years: 19% men, 29% women. EF > 50%: 39% men, 43% women. Previous CABG: 7% men, 3.8% women. Diabetes: 15% men, 20% women. Angina class I–II: 26% men, 19% women.	In-hospital only
Peterson, *et al.*, 1995 USA	Patients aged 65 years or more, from Medicare database, with CABG Retrospective, cohort 172,283 patients (from 202,488)	Groups: 65–70-year-olds (147,822) vs. 80 years old or more (24,461)	Male: 71% aged 65-70 years; 57% aged ≥ 80 years; $p < 0.01$. Mean age: 65–70-year-olds, 67 years; ≥ 80-year-olds, 82.2 years. White: 65–70-year-olds, 94%; ≥ 80-year-olds, 97%; $p < 0.01$. Diabetes: 65–70-year-olds, 16%; ≥ 80-year-olds, 8.8%; $p < 0.01$. Acute MI: 65–70-year-olds, 13%; ≥ 80-year-olds, 14%; $p < 0.01$.	3 years

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Mickleborough, *et al.*, 1995 Canada	1.1% men, 1.4% women.			3.5% men, 4.8% women.					CABG was performed in women with equally low operative mortality as men, even though women had higher incidence of co-morbid factors. Concern over increased operative mortality in women should not bias referrral patterns for angiography for CABG. More studies needed with large numbers of female patients to examine gender-specific risk factors for CABG.
Jaglal, *et al.*, 1995 Canada	3.3% total; 2.8% men, 5.3% women. Adjusted odds ratio for women vs. men, 1.55.								Women still experience higher rates of in-hospital mortality following CABG after adjustment for age, anatomical disease severity, angina class and co-morbid conditions, indicating need to further address this issue. Better understanding of natural history of coronary artery disease in women needed.
Peterson, *et al.*, 1995 USA	In-hospital: 65–70-year-olds, 4.4%, ≥ 80-year-olds, 11.5%; $p < 0.01$. 30 days: 65–70-year-olds, 4.3%; ≥ 80-year-olds, 10%; $p < 0.01$.	1 year: 65–70-year-olds 7.9%; ≥ 80-year-olds 19%; $p < 0.01$. 2 years: 65–70-year-olds 10%; ≥ 80-year-olds 24%; $p < 0.01$. 3 years: 65–70-year-olds 13%; ≥ 80-year-olds 29%; $p < 0.01$.							Present study demonstrated that use of CABG in octogenarians is expanding rapidly. Demographic changes in USA mean that decisions having growing implications for healthcare resource utilisation and national health policy.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Canver, *et al.*, 1996 USA	Armed Forces veterans who underwent their first, isolated CABG Cohort 1689 patients	Groups: ≤ 50-year-olds (213) vs. 51–70-year-olds (1258) vs. > 70-year-olds (218)	Male: 100% all groups. EF: ≤ 50-year-olds 59%; 51–70-year-olds 57%; > 70-year-olds 59%.	10 years
Fitzgibbon, *et al.*, 1996 Canada	Patients who underwent CABG at a military hospital Cohort 1388 patients	CABG	Male: > 99%. Aged ≤ 39 years, 168 (12%); 40–54 years, 954 (69%); ≥ 55 years, 267 (19%). Total SVG: 4801. Total IMA grafts: 466. Grafts/patient (average): 1st operation, 3.4; 2nd, 2.4; 3rd, 2.5.	Up to 25 years
Risum, *et al.*, 1996 Norway	Patients undergoing CABG for angina Cohort, prospective 1025 patients	Groups: diabetic (45) vs. non-diabetic (980) patients	Diabetes: 45 (4.4%). Males: 89% diabetic group; 89% non-diabetic group. 1-vessel disease: 9% diabetic, 8% non-diabetic. 2-vessel disease: 11% diabetic, 25% non-diabetic. 3-vessel disease: 80% diabetic, 66% non-diabetic. EF: 61% diabetic, 62% non-diabetic. Previous PTCA: 2% diabetic, 3% non-diabetic. Previous heart surgery: 9% diabetic, 2% non-diabetic, $p = 0.002$. Hypertension: 27% diabetic, 19% non-diabetic. Smokers: 53% diabetic, 67% non-diabetic. Unstable angina: 20% diabetic, 19% non-diabetic.	Mean 7.4 years; 7334 patient years

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Canver, *et al.*, 1996 USA	30-day mortality: aged ≤ 50 years, 1 (0.5%); 51–70 years, 13 (1%); > 70 years, 7 (3%); $p < 0.05$.	90-day: aged ≤ 50 years, 1 (0.5%); 51–70 years, 22 (2%); > 70 years, 9 (5%); $p < 0.05$. 10-year survival: aged ≤ 50 years, 74%; 51–70 years, 67%; > 70 years, 43%; $p < 0.05$.							An acceptable early mortality and long-term survival equal to those in an age-matched elderly population are sound outcome measures that help justification of CABG in older patients irrespective of age.
Fitzgibbon, *et al.*, 1996 Canada	Peri-operative rate: 2.3%. Reoperative rate: 6.6%.	Survival at: 5 years, 94%; 10 years, 81%; 15 years, 62%; 20 years, 47%; 23 years, 38%.					1 CABG, 1154; 2 CABG, 219; 3 CABG, 15. 15% repeat CABG. > 1 CABG, 17%.		Coronary bypass graft disease and occlusion common after CABG and increase with time. They are major determinants of clinical prognosis, specifically measured by reoperation rate and survival. Reoperation definitely worthwhile but entails identifiable risks that must be dealt with.
Risum, *et al.*, 1996 Norway	Odds ratio: 0.71 (0.001–5.13).	Death rate: 2.65/100 patient years. Survival at: 1 year, 93% diabetic, 95% non-diabetic; 5 years, 84% diabetic, 89% non-diabetic; 10 years, 53% diabetic, 76% non-diabetic; $p = 0.07$.		Odds ratio: 0.83 (0.31–2.11).	Postoperative MI rate: 1.39/100 patient years.				Early mortality after CABG, peri-operative MI or pump failure no more common with diabetes than without diabetes; there was no excess risk of late non-fatal MI, recurrent angina or chronic heart failure in patients with diabetes but late mortality rate was higher.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Jones & Wientraub, 1996 USA	Patients who underwent cardiac catheterisation followed by 1st time CABG for multi-vessel coronary artery disease Multicentre, cohort 2860 patients	Groups: incomplete revascularisation (803) vs. complete revascularisation (2057)	Male: 84% incomplete, 84% complete. 2-vessel disease: 27% incomplete, 47% complete, $p < 0.0001$. 3-vessel disease: 61% incomplete, 43% complete, $p < 0.0001$. Left main disease: 12% incomplete, 10% complete, $p = 0.08$. Age, years: 57 incomplete, 57 complete. EF: 57% incomplete, 60% complete, $p < 0.0001$. EF < 50%: 30% incomplete, 20% complete, $p < 0.0001$. Diabetes: 16% incomplete, 14% complete. Prior MI: 63% incomplete, 55% complete, $p = 0.0002$. Class III–IV angina: 56% incomplete, 52% complete.	Mean 12 years; 99% complete follow-up

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Jones & Wientraub, 1996 USA	1.5% incomplete, 0.7% complete, $p = 0.06$.	Survival: 1 year, 96% incomplete, 98% complete; 5 years, 87% incomplete, 92% complete; 42% 10 years, 68% incomplete, 77% complete; $p < 0.0001$. Survival curves: EF ≥ 50%, $p = 0.002$; 2-vessel disease, $p < 0.0001$; 3-vessel disease, $p = 0.006$.	Angina during follow-up: 50% incomplete, complete.	Q-wave MI: 2.9% incomplete, 2.5% complete.	Freedom from: 1 year, 93% incomplete, 95% complete; 5 years, 89% incomplete, 92% complete; 10 years: 78% incomplete, 81% complete; $p = 0.2$.		Freedom from repeat: 1 year, 99% incomplete, 99% complete; 5 years, 97% incomplete, 98% complete; 10 years, 87% incomplete, 88% complete.	Freedom from: 1 year, 99% incomplete, 99% complete; 5 years, 98% incomplete, 99% complete; 10 years, 92% incomplete, 92% complete.	Patients with complete or nearly complete revascularisation have an improved prognosis after coronary operation is clear. Thus, in the absence of compelling technical limitation, complete or nearly complete revascularisation attempted with coronary operation; it may be of less importance with angioplasty.

Health-related quality of life

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Caine, *et al.*, 1991 UK	Assessment of a series of patients admitted for CABG surgery Prospective series, single centre 100 patients	100 male patients admitted for CABG	Mean age, years: 51 (SD 6, range 37–59). 3-vessel disease: 77%. 3 or more bypass grafts: 84%.	1 year
Sjoland, *et al.*, 1996 Sweden	Assessment of series of patients admitted for CABG surgery Prospective series, single centre 2365 patients	2365 patients admitted for CABG	Not reported.	2 years

Study	Instruments used	Results	Conclusions
Caine, *et al.*, 1991 UK	NHP Working life Daily activities	NHP part I scores: Before surgery / 3 months after / 1 year after Physical mobility 18.0 / 4.4 / 4.4* Pain 21.9 / 3.5 / 4.2* Sleep 25.4 / 15.4 / 14.0* Energy 50.0 / 10.8 / 12.1* Social isolation 12.9 / 8.4 / 5.7* Emotional reactions 28.1 / 9.8 / 8.6* * $p < 0.01$ from before surgery, not significantly different from age-matched normal male population. NHP part II (% with problems): Before surgery / 3 months after / 1 year after Work 70 / 21 / 16* House 61 / 10 / 12* Social life 56 / 13 / 11* Home relationships 67 / 15 / 22* Sex life 74 / 20 / 16* Hobbies 68 / 14 / 11* * $p < 0.001$ Predictors of return to work (discriminant analysis): working preoperatively, absence of breathlessness, shorter length of time.	Improvements evident in general health state, symptoms and activity at 3 months and 1 year after CABG surgery. Interventions likely to influence outcomes included reduction in waiting times for operation, rehabilitation initiatives and more attention to quality of information given to patients waiting for operation, < 2 NHP mobility score for general population; $p < 0.001$. Predictors of return to unrestricted activity (discriminant analysis): working preoperatively, absence of breathlessness, shorter waiting time for operation, subjective quality-of-life assessment; $p < 0.001$.
Sjoland, *et al.*, 1996 Sweden	PGWB index; NHP; physical activity score (from Angina Pectoris Quality-of-life Questionnaire)	PGWB: Preoperative (SEM): 91.8 (1.0), n = 245; 2 years postoperative (SEM): 106.7 (0.9), n = 327, $p < 0.001$; Population PGWB: 104. Physical activity score: Preoperative (SEM): 4.30 (0.06), n = 245; 2 years postoperative (SEM): 2.64 (0.06), n = 327, $p < 0.001$. NHP I: improved in all domains except isolation, $p < 0.001$; NHP II: improved in all domains, $p < 0.001$. Significant association between poor performance at exercise and worse NHP before ($p < 0.001$) and after CABG ($p = 0.002$). Significant association between angina attacks and levels of distress before ($p < 0.001$) and after CABG ($p < 0.001$). Levels of distress higher for women before and after CABG ($p < 0.001$). NHP change higher for women ($p < 0.001$).	The greatest improvement in quality of life after CABG occurred in patients with most impaired exercise capacity, most severe angina pectoris, and women.

continued

Health-related quality of life *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Mayou & Bryant, 1987 UK (also Bryant & Mayou, 1989)	Assessment of series of patients admitted for CABG surgery Prospective series, single centre 79 patients	79 male patients aged over 65 years admitted for CABG	Mean age (range), years: 53.3 (32–64). Social class: I,II 27%; IIIN 13%; IIIM 32%; IV,V 29%. Previous CABG, 6%; previous MI, 58%. LVF impaired, 20%; unstable angina, 20%; on beta-blockers, 80%; claudication, 10%; left main occlusion, 8%. Number of grafts: 2 (15%), 3 (32%), 4 (43%), 5 (8%), unknown (3%). Perioperative MI (5%), CVA (6%).	1 year
Langeludecke, *et al.*, 1989 Australia	Assessment of a series of patients admitted for CABG surgery Prospective series, two centres 89 patients finally	89 patients admitted for coronary angiography who then went on to have CABG	Male: 85%. Mean age (range), years: 56 (35–75). Number of diseased vessels: 1 (12%), 2 (26%), 3 (43%), 4 (19%). 85% reported angina on exertion.	6 and 12 months

Study	Instruments used	Results	Conclusions
Mayou & Bryant, 1987 UK (also Bryant & Mayou, 1989)	Present state examination (Wing, *et al.*, 1974); Lorr-McNair self-reporting mood questionnaire (McNair, *et al.*, 1971); Wechsler Adult Intelligence Scale (Wechsler, 1955).	Severity of angina (NYHA categories) Before surgery, % — 12 months after surgery, % I — 1 — 86 II — 25 — 8 III — 49 — 5 IV — 25 — 1 Beta-blocker use reduced from 80% to 17%. Mental state: no significant change in present state examination. Lorr-McNair self-reported improvements in tension ($p < 0.001$), anxiety ($p < 0.01$), vigour ($p < 0.01$), but no change in depressed mood overall. Cognitive function did not change. Patients in lowest NYHA group at 1 year had most improvement in all five areas above. Best predictors of mental state were mental state preoperation and social class ($r = 0.51$). 'Global social outcome' predicted by limitation of physical activity, participation in leisure activities, age and severity of angina ($r = 0.53$). Functioning in early convalescence good guide to later outcome. Best predictor of return to work was preoperative work status.	Some improvements noted in mental states. 20% patients had no improvement in quality of life and this was not closely related to their physical state. Patients with 'passive' approach to their illness less likely to have good outcome.
Langeludecke, *et al.*, 1989 Australia	PAIS (Derogatis, *et al.*, 1985); Pleasant events schedule (MacPhillamy, *et al.*, 1983); CESD scale (Radloff, 1977); Spielberger State Anxiety Inventory (Spielberger, *et al.*, 1983).	Social functioning (PAIS scores): High levels of psychosocial impairment prior to surgery (58.5); significant improvement at 6 and 12 months (29.2, 30.3; $p < 0.01$). Work functioning showed trend to improved work status (NS). Domestic functioning improved significantly with surgery ($p < 0.01$). Reported sexual functioning improved significantly. Leisure interests also showed improvements. Psychological functioning: Clinical depression, before surgery, 36%; at 12 months, 22% ($p < 0.001$). Clinical anxiety, before surgery, 30%; at 12 months, 18% ($p < 0.01$). Physical outcome: Angina free, before surgery, 14%; at 12 (and 6) months, 70%.	In general, a significant reduction in psychological morbidity and an improvement in psychosocial functioning at 6 months, which remained at 12 months. Vocational and domestic function showed greatest improvement. Sexual and social function showed modest improvements overall; significant numbers reported residual impairment due to their heart disease.

continued

Health-related quality of life *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Caine, *et al.*, 1991 UK	Assessment of series of patients admitted for CABG surgery Prospective series, single centre 100 patients	100 male patients admitted for CABG	Mean age, years: 51 (SD 6, range 37–59). 3-vessel disease: 77%. 3 or more bypass grafts: 84%.	1 year
Permanyer-Miralda, *et al.*, 1991 Spain	Assessment of series of male patients with stable angina admitted for coronary angiography vs. group of male patients who had CABG surgery 6 months previously Prospective series, single centre 93 patients	Group A: stable angina admitted for coronary angiography; no MI, PTCA or CABG in last 6 months (n = 48). Group B: CABG surgery 6 months previously (n = 45)	Mean age, years: Group A 55.6, Group B 56.9. Mean EF, %: Group A 62.5, Group B 56.9.follow-up Mean exercise duration (SD), minutes: Group A 6.0 (1.9), Group B 6.5 (2.2). Negative exercise test, %: Group A 2.2, Group B 50.0. CCS class — Group A, % — Group B, %* 0 — 0 — 60.0 I — 0 — 13.3 II — 29.2 — 20.7 III — 43.7 — 6.7 IV — 27.1 — 0 * 6 months after surgery Number of diseased vessels: Group A, % — Group B, %* 1 — 27.3 — 9.3 2 — 34.1 — 25.6 3 — 38.6 — 65.1 * before surgery	Cross-sectional analysis, no

Study	Instruments used	Results	Conclusions
Caine, *et al.*, 1991 UK	NHP Working life Daily activities	NHP part I scores: Before surgery — 3 months after — 1 year after Physical mobility — 18.0 — 4.4 — 4.4* Pain — 21.9 — 3.5 — 4.2* Sleep — 25.4 — 15.4 — 14.0* Energy — 50.0 — 10.8 — 12.1* Social isolation — 12.9 — 8.4 — 5.7* Emotional reactions — 28.1 — 9.8 — 8.6* * $p < 0.01$ from before surgery not significantly different from age-matched normal male population. NHP part II (% with problems): Before surgery — 3 months after — 1 year after Work — 70 — 21 — 16* House — 61 — 10 — 12* Social life — 56 — 13 — 11* Home relationships — 67 — 15 — 22* Sex life — 74 — 20 — 16* Hobbies — 68 — 14 — 11* * $p < 0.001$ Predictors of return to work (discriminant analysis): working preoperatively, absence of breathlessness, shorter waiting time for operation, < double NHP mobility score for general population; $p < 0.001$. Predictors of return to unrestricted activity (discriminant analysis): working preoperatively, absence of breathlessness, shorter waiting time for operation, subjective quality-of-life assessment; $p < 0.001$.	Improvements evident in general health state, symptoms and activity at 3 months and 1 year after CABG surgery. Interventions likely to influence outcomes included reduction in waiting times for operation, rehabilitation initiatives and more attention to quality of information given to patients.
Permanyer-Miralda, *et al.*, 1991 Spain	NHP (Spanish version) Exercise test	NHP part I scores: Group A — Group B Physical mobility — 22.1 — 19.7 Pain — 27.9 — 19.7 Sleep — 37.0 — 26.7 Energy — 29.2 — 20.7 Social isolation — 8.7 — 10.7 Emotional reactions — 29.1 — 28.0 No significant relationship between NHP, no diseased vessels, CCS class or EF. NHP scores lower in patients with negative exercise tests. Exercise time related to pain ($p = 0.002$) and energy ($p < 0.001$) domains of NHP.	Consistency was found between functional capacity of stable coronary patients and self-perceived health status.

continued

Health-related quality of life *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
King KB, *et al.,* 1992b USA	Assessment of series of patients admitted for CABG surgery Prospective series, single centre 155 patients (316 approached)	155 patients admitted for elective CABG, > 18 years old, non-psychotic and able to communicate in English	78.7% male, 98.7% white. Mean age (range), years: 60.6 (33–80). Social class I, II, III: 66%.	1 year
Kallis, *et al.,* 1993 UK	Assessment of series of patients aged over 70 years admitted for CABG surgery Retrospective series, single centre 145 patients	145 patients over the age of 70 years admitted for CABG	Not reported separately for this group.	Mean length of follow-up: 15 months
Gold, *et al.,* 1995 USA	Assessment of patients admitted for CABG surgery and randomised to receive either high or low intra-operative mean arterial pressure Prospective RCT, single centre 248 patients	Primary, elective CABG patients receiving either high or low intra-operative MAP	High MAP / Low MAP Sex (% male): 78 / 82 Age (mean/SD), years: 66.2/10.1 / 65.4/8.6 Caucasian (%): 91 / 95 High school education or higher, %: 93 / 87 Mean EF (SD), %: 48.8 (12.7) / 47.6 (12.3) Symptom duration: mean (SD), years: 5.4 (7.7) / 5.0 (7.3) Previous PTCA, %: 6 / 10 Previous MI, %: 38 / 48 Hypertension, %: 44 / 56 Diabetes, %: 23 / 18 Cigarette smokers, %: 9 / 3 Working, %: 44 / 56 CCS class, %: I: 19 / 16 II: 25 / 23 III: 15 / 11 IV: 27 / 23	6 months.

Study	Instruments used	Results	Conclusions
King KB, *et al.,* 1992b USA	Satisfaction with life scale (Diener, *et al.,* 1985) 72-item bipolar profile of mood states (POMS-BI) (Lorr & McNair, 1982) SIP (Bergner, *et al.,* 1976) Angina severity Perception of consequence of surgery Return to work	Mean scores for satisfaction with life did not change significantly ($p = 0.07$). Positive mood scores increased, $p < 0.001$. Negative mood scores decreased, $p < 0.001$. Number of patients experiencing angina fell from 81% to 21%. Mean scores for angina severity fell, $p < 0.001$. 86% patients returned to work. 15% patients were uncertain surgery worthwhile, or did not consider it worthwhile; patients attitude to surgery was related to angina severity at 1 year, $p < 0.01$ and functional disruption (SIP), $p < 0.05$.	Functional disruption moderately-to-highly related to measures of emotional well-being, although clinical indicators such as angina do not appear to be consistently related to perceptions of outcome.
Kallis, *et al.,* 1993 UK	Rosser disability and distress scores	60 patients showed no improvement, and 87 showed improvement on the Rosser distress scale. (More results could not be used as they were combined with results obtained from valve surgery patients.)	Cardiac surgery in patients over age 70 years offers '...improvement in quality of life in the majority but... resulted in no improvement, or even deterioration in at least a third of responding patients'.
Gold, *et al.,* 1995 USA	Change in cognitive status CESD scale (Radloff, 1977); Change in quality of life (SF-36)	Low MAP / High MAP 6 month mortality, %: 4.0 / 1.6 NS Major cardiac and neurologic indices, %: 12.9 / 4.8 ($p = 0.026$) Cognitive outcome, %, deterioration at 6 months: 12 / 11 NS SF-36 ('improvement in all seven domains'; no differences between groups): Low MAP: Baseline / 6 months; High MAP: Baseline / 6 months Physical: 55 / 74 / 61 / 79 Social: 67 / 83 / 74 / 84 Role: 46 / 69 / 48 / 69 Energy: 49 / 59 / 51 / 63 Mental: 66 / 72 / 68 / 75 Pain: 62 / 82 / 63 / 79 General health: 60 / 65 / 61 / 67	Elevation of MAP during cardiopulmonary bypass effectively improves outcomes after elective CABG.

continued

Health-related quality of life *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Flynn & Frantz, 1987 USA	Assessment of series of patients in early convalescent period after CABG Prospective series, single centre 29 patients	29 men over 21 who had their first CABG operation in previous 6–10 weeks	Mean age (range), years: 58 (43–74).	No follow-up
Klonoff, *et al.*, 1989 USA	Assessment of series of patients admitted for CABG surgery and impact of surgery on intellectual and neuropsychological status Prospective series, 2 centres 135 patients (82.3% completed study)	135 patients less than 69 years old, no prior CABG, elective admissions with ischaemic heart disease	89% male. Mean age (range), years: 55.4 (35–68). CHA functional class: I 4% II 31% III 24% IV 32%	2 years
Steine, *et al.*, 1996 Norway	Assessment of series of patients admitted for CABG surgery Prospective series, single centre 213 patients (from 610 admissions)	213 elective CABG admissions	89% male. Mean age (SD), years: 61 (8.2). NHYA class, % Before surgery After surgery I 1.4 77.9 II 32.4 19.7 III 62.0 2.3 IV 4.2 0 Previous MI, %, 50.7; smoker, %, 13.1; diabetes, %, 7.5. Mean grafts per patient (SD): 3 (1).	1 year

Study	Instruments used	Results	Conclusions
Flynn & Frantz, 1987 USA	Self-anchoring scale (Cantril, *et al.*, 1965) validated 10-step non-verbal ladder device to assess life satisfaction and health perception.	Ratings: Life satisfaction Health perception Past (2 years ago) 6.51 6.03 Present 6.41 6.58 Future (2 years hence) 7.75 7.65 Health perception correlated with life satisfaction, $p < 0.001$, $r = 0.58$. All patients expected health to improve in future. Life satisfaction increased in married men and with higher socio-economic status. Patients with angina symptoms tended to rate their health lower than those without symptoms.	Quality of life enhanced for majority of patients because of relief from angina. Patients may experience a 'halo' effect from just surviving heart surgery, coupled with a sense of perceived cure.
Klonoff, *et al.*, 1989 USA	Cognitive measure: WAIS-R	At 24 months, mean increase in IQ was 6.5, $p < 0.001$.	CABG does not result in long-term deleterious or beneficial effects in intellectual and neuro-psychological functioning.
Steine, *et al.*, 1996 Norway	Family APGAR score 30-item Goldberg General Health Questionnaire	GHQ score: Before surgery After surgery Patients with mental distress 38% 23% ($p < 0.0001$) 69% patients reported lower GHQ scores (enhanced well-being); 37% reported higher or the same scores. Psychological well-being was related to NYHA class ($p = 0.005$). Sex affected well-being in multivariate analysis.	Most patients reported significant improvement in physical and psychosocial functioning 1 year after CABG. Mental distress and male sex were significant predictors of enhanced well-being.

Cost and cost-effectiveness (primary studies)

Study	Design	Baseline characteristics	Selection criteria	Methods
Dougenis, *et al.*, 1992 UK	Retrospective, single centre, bottom-up cost analysis of cohort of CABG patients to assess costs associated with re-CABG.	CABG (n = 49); 90% male. Mean age (SD, range), years: 53.6 (7.95, 42–67). Mean time since 1st CABG: 68.2 months (SD, 37.1). Reasons for re-CABG: graft failure, 30.5%; incomplete revascularisation, 4.1%; new disease, 14.3%, patent but atherosclerotic graft disease, 20.4%. Combination: 30.6%. 3-vessel disease: 55.1%.	Patients undergoing re-CABG; angina refractory to medical treatment.	Perspective: partial health service (hospital). Patients included: 15 randomly selected undergoing elective 1st time CABG, 5 undergoing re-CABG. Based on hospital costs for recatheterisation; excludes GP visits, outpatient visits, travel costs. Expressed in 1988, 89, 90 £UK; sources of costs reported.

Study	Follow-up (duration of costing)	Results	Conclusions
Dougenis, *et al.*, 1992 UK	Mean 3.7 years (range 0.8–9.0).	1st time CABG cost estimated by Hospital General office: £3645 (1989/90). 1st time CABG estimated in 15 patients: £4049 (1989/90). Reoperation estimated in 5 consecutive cases: £7235 (1989/90).	Repeated CABG surgery appears to be 1.8 times more expensive than 1st time CABG, carries twice the mortality rate and is associated with a 50% net decrease in overall rehabilitation status.

Appendix 9

Summary table of medical adjuncts to CABG: clinical effectiveness

Clinical effectiveness

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Oka, *et al.*, 1980 USA	Patients scheduled for elective CABG and receiving long-term propranolol. RCT 54 patients + 17 not receiving propranolol	Groups: (1) no propranolol; n = 17. (2) propranolol stopped 48 hours pre-surgery; n = 17. (3) propranolol stopped 10 hours pre-surgery; n = 18. (4) propranolol continued post-surgery for 36–48 hours (n = 19).	Male: Group 1, 65%; 2, 65%; 3, 67%; 4, 58%. Mean age, years: Group 1, 59; 2, 53; 3, 55; 4, 56. Previous MI: Group 1, 23%; 2, 23%; 3, 28%; 4, 26%. Grafts/patient: Group 1, 2.3; 2, 2.3; 3, 2.4; 4, 2.5.	In-hospital only.
Mayer, *et al.*, 1981 USA	Patients undergoing CABG for refractory angina. RCT 113 patients	Groups: 650 mg aspirin + 50 mg dipyridamole b.d. (n = 47) vs. control group (n = 66).	Male: 77% treated, 86% controls. Mean age, years: 56.2 treated, 52 controls. Grafts/patient: 1.9 treated, 1.9 controls.	3–6 months.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Oka, *et al.*, 1980 USA	Group 2, 1 (6%).			Group 1, 1 (6%); 2, 3 (18%); 3, 1 (6%); 4, 0.					Propranolol should not be abruptly withdrawn even as early as 10 hours before surgery. Gradual withdrawal of therapy prior to surgery not well-resolved but, in absence of apparent complications from continual propranolol therapy, little justification exists for even gradual withdrawal.
Mayer, *et al.*, 1981 USA						Total: 94% treated, 82% controls, $p < 0.02$. SVG: 92% treated, 78% controls, $p < 0.02$. IMA: 100% treated, 96% controls.			Improvement in patency with aspirin and dipyridamole present when groups were broken down by gender, vessel grafted or by patients with patent grafts. Two groups not identical. On basis of study, authors continue to administer aspirin + dipyridamole to patients after CABG hoping for improved patency rates.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
McEnany, *et al.*, 1982 USA	Patients who had 1–4 SVGs. RCT, double-blind (except for warfarin) 216 patients	Groups: 2 × 300 mg aspirin b.d. (n = 71) vs. warfarin (n = 68) vs. placebo (n = 77).	Male: 87% placebo, 82% aspirin, 93% warfarin. Age 20–30 years: 1.8% placebo, 2% aspirin, 0% warfarin. Age 31–40 years: 5.4% placebo, 6% aspirin, 11% warfarin. Age 41–50 years: 40% placebo, 44% aspirin, 32% warfarin. Age 51–60 years: 40% placebo, 38% aspirin, 48% warfarin. Age 61–70 years: 13% placebo, 10% aspirin, 9% warfarin. Diabetes: 13% placebo, 14% aspirin, 20% warfarin. NYHA class III or IV: 82% placebo, 82% aspirin, 84% warfarin. Stable angina: 62% placebo, 80% aspirin, 70% warfarin.	1 year; 22 (29%) placebo group; 21 (30%) aspirin group; 12 (18%) warfarin group.
Myhre, *et al.*, 1984 Norway	Patients undergoing CABG for stable angina treated with beta blockade. RCT 40 patients	Groups: (1) beta-blocker stopped 12 hours before CABG (n = 20) vs. (2) beta-blocker stopped 2 hours before CABG, then propranolol (20 mg/ 6 hourly) given for 8 days (n = 20).	Male: 85% routine, 75% propranolol. Number of vessels involved: 2.7 routine, 2.4 propranolol. EF: 65.4% routine, 67.4% propranolol. Grafts/patient: 3 routine, 2.7 propranolol.	8 days; four excluded from propranolol.
Brown, *et al.*, 1985 USA	Male patients eligible for CABG, aged 34–70 years. RCT, double-blind 147 patients	Groups: (1) 325 mg aspirin + 75 mg dipyridamole t.d.s. (n = 49). (2) 325 mg aspirin + dipyridamole placebo (n = 47). Double placebo, as above (n = 51). Taken for 1 year.	None given.	1 year; 7 placebo group, 9 aspirin only group (3 from side-effects), 4 aspirin + dipyridamole (1 from side-effects). Includes 1 death in each group.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
McEnany, *et al.*, 1982 USA		Fatal MI: 3 (5%) placebo, 1 (1.4%) aspirin.	NYHA class I. 83 placebo, II. 11 aspirin, I. 23 warfarin ($p < 0.01$).		Nonfatal: 2 (4%) placebo, 1 (1.5%) warfarin.	All grafts patent: 57% placebo, 63% aspirin, 71% warfarin.			Results of study suggest short-term antithrombotic therapy deserves further assessment in prevention of vein graft occlusion in first year or two following CABG. This potential benefit must be evaluated in context of recognised bleeding complications of warfarin therapy.
Myhre, *et al.*, 1984 Norway				1 routine, 1 propranolol.					Study fails to demonstrate significant reduction in occurrence of postoperative clinically important SVA. Administration of low doses of propranolol immediately pre- and post-CABG requires further investigation.
Brown, *et al.*, 1985 USA		One death in each group.				All grafts patent: Group 1, 67%; 2, 74%; 3, 59%.			Data support position that aspirin, begun within 48 hours of operation, provides substantial benefit with respect to graft patency, particularly in patients with grafts with good flow supplying larger arteries. Study does not directly exclude possibility of added benefit from preoperative dipyridamole continued postoperatively with aspirin.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Rajah, *et al.*, 1985 UK	Patients referred for CABG for angina and stenosis of ≥ 70%. RCT, double-blind 103 patients	Groups: 330 mg aspirin + 75 mg dipyridamole t.d.s. (n = 48) vs. placebo (n = 55). Taken for 6 months.	1-vessel > 70% stenosis: 19% treatment, 25% placebo. 2-vessel > 70% stenosis: 42% treatment, 49% placebo. ≥ 3-vessel > 70% stenosis: 39% treatment, 25% placebo. Mean age, years: 49 treatment, 49 placebo. Age > 50 years: 54% treatment, 53% placebo. Smoking: 69% treatment, 65% placebo. Previous MI: 42% treatment, 47% placebo.	6 months; mean 6.5 months. 13 aspirin + dipyridamole group (2 side-effects), 9 placebo (1 side-effects).
Gershlick, *et al.*, 1988 UK	Patients undergoing CABG. RCT, blind? 320 patients	Groups: 330 mg aspirin + 75 mg dipyridamole t.d.s. (n = 160) vs. placebo (n = 160).	Male: 89% placebo, 87% treatment. Mean age, years: 54.5 placebo, 54.2 treatment. Hypertension: 22% placebo, 20% treatment. Diabetes: 4% placebo, 9% treatment. Angina grade 2: 29% placebo, 36% treatment; grade 3: 27% placebo, 21% treatment; grade 4: 37% placebo, 41% treatment. 1 artery > 75% stenosis: 26% placebo, 19% treatment. 2 arteries > 75% stenosis: 36% placebo, 34% treatment. 3 arteries > 75% stenosis: 37% placebo,47% treatment.	Mean 6.6 years; 87.7% (250) had outpatient interview.
van der Meer, *et al.*, 1993 The Netherlands	Patients with disabling angina who underwent CABG with SVGs. RCT, double-blind, multicentre 948 patients	Groups: (1) 50 mg aspirin + placebo (n = 317) (2) 50 mg aspirin + 200 mg dipyridamole (n = 313) (3) oral anticoagulants (4 mg acenocoumarol or 6 mg phenprocoumon).	Male: Group 1, 87%; 2, 85%; 3, 88%. Mean age, years: Group 1, 58; 2, 59; 3, 58. Previous MI: Group 1, 56%; 2, 52%; 3, 52%. Diabetes: Group 1, 8%; 2, 11%; 3, 10%. NYHA class III/IV: Group 1, 67%; 2, 70%; 3, 69%.	1 year; 86% repeat angiograms. Dropouts: 15% Group 1, 19% Group 2, 17% Group 3.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Rajah, *et al.*, 1985 UK		One death in each group.				92% treatment, 75% placebo, $p < 0.01$.			Study shows that an antiplatelet regimen of 330 mg of aspirin in combination with 75 mg of dipyridamole t.d.s., significantly improves early patency rate of aorta-coronary saphenous vein bypass grafts.
Gershlick, *et al.*, 1988 UK		All causes: 35 (10.9%). Cardiac: 13 (8.1%) treatment; 8.7% placebo.	49 (31%) treatment; 45 (28%) placebo.		7 (4.3%) treatment, 2 (1.2%) placebo.		5 (3.1%) treatment, 5% placebo.		Aspirin and dipyridamole results confirm that, provided early thrombolytic occlusion is prevented, these antiplatelet drugs confer no long-term clinical benefit. Clearer understanding of pathophysiology of graft failure and better antiplatelet drugs needed.
van der Meer, *et al.*, 1993 The Netherlands	Peri-operative: Group 1, 0.6%; 2, 1%; 3, 0.3%.	Group 1, 2.6%; 2, 1.7%; 3, 1%.	Group 1, 14%; 2, 18%; 3, 19%.	Group 1, 7.4%; 2, 8.1%; 3, 6.5%.	Group 1, 8.1%; 2, 9.8%; 3, 7.8%.				Data provide no convincing evidence that addition of dipyridamole to low dose of aspirin improves 1-year vein-graft patency after CABG surgery. Combination of these drugs associated with increase in overall clinical-event rate. Oral coagulants, compared with aspirin, provided no benefit.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Azen, *et al.*, 1996 USA	Men with previous CABG initally randomised to colestipol/niacin plus cholesterol lowering diet, or placebo plus diet. 162 patients completed follow-up	Colestipol/niacin plus cholesterol lowering diet (n = 80) vs. placebo plus diet (n = 82).	No significant differences reported between groups at baseline.	Annual follow-up for average of 7 years.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Graft patency	CABG	Re-PTCA	Conclusions
Azen, *et al.*, 1996 USA		Non-fatal MI or coronary death lower in treatment group: RR = 0.4; $p = 0.02$.			All coronary events lower in treatment group: RR = 0.6; $p = 0.04$.				Limitation of study highlighted by authors is that patients were all non-smoking, middle-aged men with previous CABG; difficult to generalise from this to likely effects of lipid-lowering therapy on progression of coronary artery disease.

Appendix 10

Summary tables of non-comparative observational studies of PTCA only

Clinical effectiveness

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Bentivoglio, 1985 USA	NHLBI Registry and patients from three other hospitals with 1-vessel disease. Registry, cohorts 3590 patients (NHLBI 1979–82; others 1983–84)	PTCA. Groups: NHLBI registry (1939) vs. Atlanta, Richmond and Philadelphia (others) (1551).	Diameter stenosis before PTCA: 84% NHLBI, 75% others. Diameter stenosis after PTCA: 31% NHLBI, 26% others.	1 year (mean 550 days); 987 (51%) NHLBI follow-up, other cohorts less complete.
Ernst, *et al.*, 1987 The Netherlands	Patients who responded poorly to medication and followed-up over 6 months. Cohort 1352 patients (of 1889)	PTCA.	Male: 80%. 1-vessel disease: 70%. Normal EF: 55%. Previous CABG: 82 (6%). Previous PTCA: 113 (9%). Angina III or IV: 72%.	5 years, all > 6 months.
McEniery, *et al.*, 1987 USA	Patients having PTCA. Cohort 3696 patients	PTCA. Groups: women (2727) vs. men (969).	Mean age, years: 61 women, 57 men. Stable angina: 20% women, 22% men. Prior PTCA: 13% women, 15% men. Prior CABG: 9% women, 15% men; $p = 0.0005$. Diabetes: 19% women, 11% men; $p = 0.0005$. Smoker: 53% women, 74% men; $p = 0.0005$.	6 months; 90% women and 94% men followed-up.
Hartzler, *et al.*, 1988 USA	Patients having PTCA with at least one high risk factor. Cohort 6500 patients	PTCA. Groups: left main disease, 103; EF ≤ 40%, 664; age ≥ 70 years, 1038; 3-vessel disease, 305; unstable, 193; acute MI, 446; multi-lesion, 3612; prior CABG, 1225.	Left main disease: 1.6%. Unstable 3%. EF ≤ 40%: 10%. Age ≥ 70 years: 16%. 3-vessel disease: 4.7%. Acute MI: 6.9%. Multi-lesion: 56%. Prior CABG: 19%.	3 years.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Bentivoglio, 1985 USA	0.8% NHLBI, 0.1% others.		Recurrence 19% in other cohort.	3.1% NHLBI, 0% others.		33% NHLBI.	10% NHLBI.	13% NHLBI.	Success rate improved dramatically and complication decreased, but restenosis hardly changed.
Ernst, *et al.*, 1987 The Netherlands	10 (0.7%).	16 cardiac deaths (1.4%); 6 non-cardiac deaths (0.5%).	At 5 years, 74% stable angina patients free from symptoms.	29 (2.1%).	11 (0.9%).	*et al.*, 1987	At follow-up 58 (5%) had CABG.	93 (8%); 13 (1%) had PTCA in other segments.	Angiographically successful angioplasty offers better chance of long-lasting symptom relief than previously suggested. If restenosis occurs second PTCA can be performed with good initial and late results.
McEniery, *et al.*, 1987 USA	0.3% women, 0.1% men.				2.9% women, 2% men.	27% women, 29% men.	Late CABG: 7% women, 6.8% men.	4.9% women, 5.3% men.	PTCA in women does not carry increased complication rate and has good long-term success rate compared with men.
Hartzler, *et al.*, 1988 USA	Total, 0.7%; 1-lesion, 0.6%; multi-lesion, 0.8%; prior CABG, 0.9%; left main disease, 3.9%; EF ≤ 40%, 2.7%; age ≥ 70 yrs, 1.4%; unstable, 1.5%; all 3 vessels, 1.3%.	Left main disease, 8%; age 80–92 yrs, 24%; unstable, 4%. 3-year survival: 90% multi-lesion; 87% left main disease; age ≥ 70 yrs, 94%; 1-/2-vessel disease, 56%; 3-vessel disease, 91% unstable.		Total, 0.5%; 1-lesion, 0.4%; multi-lesion, 0.6%; prior CABG, 0.6%; left main disease, 0.9%; EF ≤ 40%, 0.7%; age ≥ 70 years, 0.8%; unstable, 1.5%; all 3 vessels, 0.6%.	Left main disease, 4%; age 80–92 years, 1.4%; unstable, 2%.		Left main disease, 12%; age 80–92 years, 13%, multi-vessel and lesion, 16%; unstable 10%.	Multi-vessel and lesion, 23%.	Management of high-risk patients must be individualised.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Yamaguchi, 1990 Japan	Patients undergoing successful elective PTCA. Cohort 1149 patients (1206 including emergency procedures)	PTCA. Groups: 1-vessel disease (620) vs. multi-vessel disease (586).	Male: 975 (81%). Age > 70 years: 203 (17%). Previous CABG: 8%. Angina III or IV: 348 (29%). PTCA 1-vessel: 43 (40%). PTCA culprit lesion only: 45/65 (69%).	Average 31 months; 566 patients followed-up, 99% complete.
Bentivoglio, *et al.*, 1991 USA	Patients undergone PTCA for multi-vessel disease and stable or unstable angina. NHLBI PTCA Registry 1985–86 1720 patients	PTCA. Groups: unstable (952) vs. stable angina (768).	Male: 78% stable, 69% unstable, $p < 0.001$. Age ≥ 65 years: 24% stable, 29% unstable, $p < 0.01$. 1-vessel disease: 47% stable, 46% unstable. 1-vessel, 1-lesion disease: 33% stable, 33% unstable. EF < 50%: 23% stable, 15% unstable, $p < 0.001$. Diabetes: 11% stable, 16% unstable, $p < 0.01$.	2 years; 14 patients lost to follow-up.
Stevens, *et al.*, 1991 USA	Patients having PTCA not acute MI. Cohort 8962 procedures	PTCA. Groups: LVD, EF ≤ 40% (704 patients, 845 procedures) vs. no LVD, EF > 40% (8117 procedures).	Male: 79% LVD, 78% no LVD. Mean age, years: 63 LVD, 60 no LVD, $p < 0.01$. 1-vessel disease: 10% LVD, 32% no LVD, $p < 0.001$. Diabetes: 25% LVD, 14% no LVD, $p < 0.001$. NYHA class III or IV: 67% LVD, 63% no LVD, $p < 0.001$. 1 artery narrowed ≥ 70%: 12% (507) calculated, 7% (338) estimated LVD. 2 arteries narrowed ≥ 70%: 29% calculated, 25% estimated LVD. 3 arteries narrowed ≥ 70%: 59% calculated, 68% estimated LVD, $p = 0.01$. Multi-lesion PTCA: 67% LVD, 62% no LVD, $p = 0.005$. Multi-vessel PTCA: 45% LVD, 42% no LVD.	≥ 6 months; 6 patients lost to follow-up.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Reste-nosis	CABG	Re-PTCA	Conclusions
Yamaguchi, 1990 Japan	1-vessel disease 0%, multi-vessel disease 0.7%.	1-vessel disease 1.3%, multi-vessel disease 2%. 4-year survival: 1-vessel disease 98%, multi-vessel disease 98%.	1-vessel disease 11%, multi-vessel disease 22%, $p < 0.01$.	1-vessel disease 1.1%, multi-vessel disease 1%.	1-vessel disease 3%, multi-vessel disease 4%.		1-vessel disease 1.3%, multi-vessel disease 3.9%, $p < 0.05$.	1-vessel disease 28%, multi-vessel disease 37%, $p < 0.05$.	PTCA could be used as 1st choice for all 1-vessel disease but only in selected patients with multi-vessel disease. Restenosis most significant problem limiting effectiveness of PTCA.
Bentivoglio, *et al.*, 1991 USA	1.5% in both groups.	Survival: 96% stable, 95% unstable.			2% in both groups.		Emergency CABG (in-hospital): 2% stable, 4% unstable, $p < 0.05$.	Both groups, 1st year 18%, 2nd year 2%.	Same rate of immediate success and long-term freedom from untoward events. PTCA indicated for relief of stenosis in properly selected patients with 1- or multi-vessel disease in unstable angina.
Stevens, *et al.*, 1991 USA	5% LVD, 1% no LVD, $p < 0.001$.	1-year survival: 87%. 4-year survival: 69%.	Class III or IV: 15%.		8%		15%	27%	PTCA may be effective treatment for coronary artery disease in patients with LVD.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Weintraub, *et al.*, 1993a USA	Patients who had successful elective PTCA for angina with no prior PTCA or CABG and no in-hospital complications. Cohort, model 2500 patients	Groups: no restenosis (1355) vs. restenosis (1145).	Male: 76% no restenosis, 78% restenosis. Mean age, years: 57 no restenosis, 58 restenosis, $p = 0.015$. Multi-vessel disease: 26% no restenosis, 28% restenosis. Multi-site: 22% no restenosis, 23% restenosis. Diameter stenosis pre-PTCA: 73% no restenosis, 76% restenosis, $p < 0.0001$. Diameter stenosis on restudy: 26% no restenosis, 74% restenosis, $p < 0.0001$. Lesion length: 6.8 mm no restenosis, 6.9 mm restenosis. EF: 59% no restenosis, 58% restenosis. Angina class III or IV: 53% no restenosis, 64% restenosis, $p < 0.0001$. Diabetes: 11% no restenosis, 15% restenosis, $p = 0.0033$.	None.
Weintraub, *et al.*, 1993b USA	Patients who had successful PTCA with no previous PTCA or CABG; restudy 4–12 months after initial PTCA. Prospective, cohort 3363 patients (47% of 8668)	PTCA groups: restenosis (1570) vs. no restenosis (1793).	Male: 77% both groups. Mean age, years: 56 no restenosis, 57 restenosis, $p < 0.0001$. Multi-vessel disease: 23% no restenosis, 29% restenosis, $p = 0.0001$. Multi-site PTCA: 15% no restenosis, 24% restenosis, $p < 0.0001$. Diameter stenosis: 73% no restenosis, 76% restenosis, $p < 0.0001$. Diameter stenosis post-PTCA: 23% no restenosis, 25% restenosis, $p < 0.0001$. EF < 50%: 14% no restenosis, 16% restenosis. Diabetes: 10% no restenosis, 14% restenosis, $p = 0.0001$. Angina class III or IV: 50% no restenosis, 60% restenosis, $p < 0.0001$.	Mean 3.8 years; 97% complete > 1 year follow-up.
Surya-pranata, *et al.*, 1993 The Netherlands	Patients who underwent monorail technique for PTCA. Cohort 2183 patients	Groups: stable (1288) vs. unstable angina (720).	Male: 78%. 1-vessel disease: 66%. Mean age, years: 58. EF < 45%: 8%. Prior CABG: 12%. Stable angina: 59%. 1-vessel/lesion: 74%. 1-vessel/multi-lesion: 11%. Multi-vessel/lesion: 15%.	Mean 22 months.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Reste-nosis	CABG	Re-PTCA	Conclusions
Weintraub, *et al.*, 1993a USA	Multi-vessel correlates of restenosis are: angina class III or IV ($p < 0.0001$), pre-PTCA diameter stenosis > 70% ($p < 0.0001$), proximal LAD lesion ($p < 0.0001$), diabetes ($p = 0.0033$), post-PTCA diameter stenosis < 30% ($p = 0.0037$), hypertension ($p = 0.015$), no intimal tear ($p = 0.042$), age < 60 years ($p = 0.015$).								Not possible to predict restenosis will occur. Possible to predict probability of restenosis (with uncertainty) in well-characterised patients.
Weintraub, *et al.*, 1993b USA		1-year survival: 99% no restenosis, 99% restenosis. 6-year survival: 95% no restenosis, 93% restenosis.	Angina: 39% no restenosis, 71% restenosis, $p < 0.0001$.		1 year free from MI: 96% no restenosis, 92% restenosis. 6 years free from MI: 88% no restenosis, 85% restenosis, $p = 0.0001$.		1 year free from CABG: 98% no restenosis, 86% restenosis. 6 years free from CABG: 94% no restenosis, 78% restenosis, $p < 0.0001$.	1 year free from PTCA: 93% no restenosis, 25% restenosis. 6 years free from PTCA: 76% no restenosis, 20% restenosis, $p < 0.0001$.	Patients with restenosis more likely to have recurrent angina. Little difference in survival, but difference in MI rate. Principal events in restenosis group are frequent repeat revascularisations, which may be related to low MI and death rates in that group.
Surya-pranata, *et al.*, 1993 The Netherlands	Stable 0.2%, unstable 0.8%.	2%.		Stable 1.5%, unstable 3.6%.	6%.		Emergency CABG: 1.7% stable, 2.8% unstable. Follow-up: 7%	12%.	Despite significant improvement in PTCA equipment and operator skill, some problems such as abrupt occlusion and restenosis remain as major limitations of PTCA procedure.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Kelsey, *et al.*, 1993 USA	Patients undergoing first PTCA from NHLBI Registry 1985/86 (excluding acute MI patients). Cohort, registry 2136 patients	PTCA groups: women (546) vs. men (1590).	Mean age, years: 56.5 men, 61 women, $p < 0.001$. 1-vessel disease: 49% men, 48% women. 1 discrete lesion: 47% men, 48% women. Multiple discrete lesion: 8% men, 6% women, $p < 0.05$. ≥ 2 lesions attempted: 38% men, 36% women. ≥ 2 vessels attempted:26% men, 21% women. EF ≥ 50%: 79% men 86% women, $p < 0.01$. Prior CABG: 13% men 10% women. Black: 2.4% men 7.1% women, $p < 0.001$. Diabetes: 11% men, 20% women, $p < 0.001$. Angina class III or IV: 23% men, 23% women, $p < 0.001$.	4 years; 95% follow-up.
Bell, *et al.*, 1993; 1995 USA	Patients undergoing emergency or elective PTCA. Cohort 3027 patients	PTCA groups: men (2203) vs. women (824).	Mean age, years: 61 men, 66 women, $p < 0.001$. 1-vessel disease: 32% men, 34% women. EF: 60% men, 63% women, $p < 0.001$. Prior CABG: 15% men, 9% women, $p < 0.001$. Diabetes: 11% men, 19% women, $p < 0.001$. Angina class III or IV: 63% men, 78% women, $p < 0.001$. Unstable angina: 67% men, 76% women, $p = 0.01$.	Mean 5.5 years.
Topol, *et al.*, 1993a USA	Patients on insurance-claims database who had PTCA, aged < 65 years, and not on Medicare, Medicaid or Worker's Compensation. Cohort, database 2101 patients	Groups: men (1664) vs. women (437).	Mean age, years: 54 men, 55 women, $p = 0.0009$. 1-vessel PTCA: 96% men, 97% women. Length of stay, days: 5.9 men, 7.3 women, $p = 0.0001$. Prior PTCA: 3% men, 5% women. Stable angina: 72% men, 83% women, $p = 0.02$. Exercise test: 30% men, 25% women, $p = 0.02$.	Average 332 days.
Thompson, *et al.*, 1993 USA	Patients aged ≥ 65 years having urgent, elective PTCA with acute MI or totally occluded vessels. Prospective, cohort 982 patients	PTCA; all patients aged over 65 years.	Male: 62%. 1-vessel disease: 47%. Mean age, years: 71.9. Prior CABG: 15%. Angina class III or IV: 66%. Multi-vessel PTCA: 34%.	Mean 25 months.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Reste-nosis	CABG	Re-PTCA	Conclusions
Kelsey, *et al.*, 1993 USA	0.3% men, 3% women, $p < 0.001$.	Deaths at 4 years: 7% men, 11% women, $p < 0.001$.	Angina class III or IV: 3.8% men, 6% women, $p < 0.001$.	4.3% men, 4.6% women.	12% men, 12% women.		At follow-up: 18% men, 16% women.	At follow-up: 26% men 24% women.	Women have higher procedural mortality risk, explained partly by worse cardiovascular risk factor profile. Success rate and long-term prognosis after PTCA excellent; should be considered for women in need of revascularisation.
Bell, *et al.*, 1993; 1995 USA	Early cohort: 2.2% men, 2.9% women. Late cohort: 3.1% men, 5.4% women, $p = 0.01$.	10 years survival: 78% men, 73% women, $p = 0.06$.	No angina at 10 years: 37% men, 34% women, $p = 0.008$.	Early cohort: 2.4% men, 1.4% women. Late cohort: 0.6% men, 0.7% women.			33% men, 29% women, $p = 0.06$.		Long-term outcome for women similar to that for men in respect of survival and incidence of MI. Only major difference is greater use of subsequent CABG in men compared with women.
Topol, *et al.*, 1993a USA					5.4% men, 4.9% women.		14% men, 18% women.	18% men, 19% women.	Analysis highlights large proportion of patients without objective definition of myocardial ischaemia undergoing procedure, and variability in sex, geographical location and academic status of hospital sites.
Thompson, *et al.*, 1993 USA	3.2%.	9.2%.	Severe recurrent angina 26.6%.	3.7%.	4.8%.		In-hospital: 7.8%. Follow-up: 10.6%.	In-hospital: 5.6%. Follow-up: 15.4%.	PTCA appears to be attractive option in elderly patients; these results identify subgroups of patients in whom this approach appears to be particularly appropriate.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Lindsay, *et al.*, 1994a USA	Patients receiving PTCA procedure but not as treatment for MI. Retrospective, cohort 3725 procedures (77% of 4855)	PTCA.	Male: 2648 (71%). Mean age, years: 62.4. ≥ 2-lesion PTCA: 34%. Prior CABG: 25%, $p = 0.011$. Unstable angina: 62%. Type-A lesion: 12%. Type-B lesion: 34%. Type-C lesion: 54%. SVG: 11%.	Only in-hospital results.
Weintraub, *et al.*, 1994 USA	Elective PTCA for stable and unstable angina with out previous CABG or PTCA. Cohort, prospective 10,785 patients	PTCA groups: women (2845) vs. men (7940).	Mean age, years: 62 women, 57 men, $p < 0.0001$. Body surface area: 1.7 m^2 women, 2.0 m^2 men, $p < 0.0001$. Multi-vessel disease: 25% women, 31% men, $p < 0.0001$. Multi-site PTCA: 21% women, 24% men, $p = 0.0028$. Diameter stenosis pre-PTCA: 74.7% women, 75.4% men, $p = 0.018$. EF: 59% women, 58% men, $p < 0.0001$. Diabetes: 19% women, 12% men, $p < 0.0001$. Angina grade III or IV: 71% women, 58% men, $p < 0.0001$.	Mean 3.5 years; 9910 (92%) followed-up.
Arnold, *et al.*, 1994 USA	Patients undergoing first PTCA but not for acute MI. Prospective, cohort 5000 patients	Groups: women (1274) vs. men (3726).	Mean age, years: 61.5 women, 57.1 men, $p < 0.0001$. Multi-vessel PTCA: 15% women, 16% men. LVD moderate/severe: 9% women, 12% men, $p = 0.012$. Prior CABG: 10% women, 15% men, $p < 0.0001$. Diabetes: 20% women, 12% men, $p < 0.0001$. Angina class III or IV: 58% women, 42% men, $p < 0.0001$.	Median 4 years; follow-up 97.4% complete.
Lindsay, *et al.*, 1994b USA	Patients undergoing PTCA but not during evolving MI. Prospective, cohort 3199 patients	PTCA groups aged: < 55 years (815), 55–64 years (914), 65–74 years (996), ≥ 75 (474).	Male (age group): 80% (< 55), 77% (55–64), 65% (65–74), 56% (≥ 75); $p < 0.001$. ≥ 2 lesions: 30% (< 55), 37% (55–64), 34% (65–74), 38% (≥ 75); $p = 0.005$. Most complex lesion ($p = 0.034$) – type C: 52% (< 55), 53% (55–64), 52% (65–74), 60% (≥ 75). Prior CABG: 17% (< 55), 28% (55-64), 27% (65-74), 26% (≥ 75); $p < 0.001$. Unstable angina: 58% (< 55), 58% (55–64), 59% (65–74), 71% (≥ 75); $p = 0.001$.	Not specified: 68.6% procedures followed-up.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Reste-nosis	CABG	Re-PTCA	Conclusions
Lindsay, *et al.*, 1994a USA	32 (0.9%).			19 (< 1%).			Emergency: 102 (2.7%).	Emergency: 64 (1.7%).	The risk of complication of vascular access increases dramatically with age. Age is most important risk factor for need of transfusion and surgical repair, even after adjusting for other factors.
Weintraub, *et al.*, 1994 USA	0.7% women, 0.1% men, $p < 0.0001$.	5 years survival: 92% women, 95% men, $p = 0.0002$.	40% women, 27% men, $p < 0.0001$.	1% women, 0.7% men.	5 years freedom from MI: 89% women, 88% men.		5 years freedom from CABG: 85% women, 84% men, $p = 0.04$.	5 years freedom from PTCA: 67% women, 66% men, $p = 0.009$.	Despite higher in-hospital mortality, long-term mortality and clinical outcome similar for both genders when age and body habits accounted for.
Arnold, *et al.*, 1994 USA	1.1% women, 0.3% men, $p = 0.001$.	93% survival.		0.4% women, 0.4% men.			In-hospital: 5% women, 4.5% men.		Despite higher risk profile, womens' overall and event-free survival better than mens'. Male gender is risk factor for repeat PTCA, which suggests gender difference in favour of females for long-term, event-free survival.
Lindsay, *et al.*, 1994b USA	0.5% aged < 55, 0.5% 55–64, 1.1% 65–74, 2.1% ≥ 75; $p = 0.014$.			0% aged < 55, 0.3% 55–64, 0.5% 65–74, 1.3% ≥ 75; $p = 0.01$.			In-hospital emergency CABG: 2.1% aged < 55, 3.7% 55–64, 2.2% 65–74, 3.6% ≥ 75; $p = 0.082$.	In-hospital: 2% aged < 55, 2.1% 55–64, 1.1% 65–74, 2.3% ≥ 75.	Risk of complication of vascular access dramatically increases with age. Age is most important risk factor for need of transfusion and surgical repair, even after adjusting for other factors.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Richardson, *et al.*, 1994 Australia	Patients undergoing PTCA. Prospective, cohort 2571 patients	PTCA groups: age < 75 years (2483) vs. age ≥ 75 years (88).	Males: 59% ≥ 75, 77% < 75, $p < 0.001$. Mean age, years: 78.2 ≥ 75, 57.5 < 75. 1-vessel disease: 24% ≥ 75. Prior CABG: 11% ≥ 75, 6% < 75, $p < 0.05$. Diabetes: 13% ≥ 75. Angina class III or IV: 96% ≥ 75, 78% < 75, $p < 0.001$. Urgent procedures: 39% ≥ 75, 14% < 75, $p < 0.001$.	≥ 6 months (average 20 months) and only for ≥ 75-year-olds.
Scott, *et al.*, 1994 USA	NHLBI Registry patients who had PTCA for first time and were either white or black. Cohort 2015 patients	PTCA groups: black patients (76) vs. white (1939).	Male: 50% black, 76% white, $p < 0.001$. Age ≥ 65 years: 20% black, 27% white, $p < 0.05$. EF < 50%: 15% black, 18% white. 1-vessel disease: 28% black, 50% white, $p < 0.001$. 1-lesion PTCA: 57% black, 63% white. 1-vessel PTCA: 76% black, 80% white. Diameter stenosis: 85% black, 81% white, $p < 0.01$. Prior CABG: 10% black, 12% white. Diabetes: 23% black, 13% white, $p < 0.05$. Angina class III or IV: 72% black, 52% white.	5 years; 89% complete follow-up.
Weintraub, *et al.*, 1995b USA	Patients undergoing first PTCA with no previous CABG. Registry 10,783 patients	PTCA groups: 1-vessel disease (7604), 2-vessel disease (2587), 3-vessel disease (592).	Male: 1-vessel disease 72%, 2-vessel disease 77%, 3-vessel disease 79%, $p < 0.0001$. Mean age, years: 1-vessel disease 57, 2-vessel disease 59, 3-vessel disease 62, $p < 0.0001$. EF: 1-vessel disease 59%, 2-vessel disease 56%, 3-vessel disease 56%, $p < 0.0001$. Angina III or IV: 1-vessel disease 61%, 2-vessel disease 64%, 3-vessel disease 66%, $p = 0.0015$. Multi-site: 1-vessel disease 15%, 2-vessel disease 43%, 3-vessel disease 52%, $p < 0.0001$. 1 vessel dilated ($p < 0.0001$): 1-vessel disease 99%, 2-vessel disease 69%, 3-vessel disease 66%. 2 vessels dilated: 1-vessel disease 1%, 2-vessel disease 30%, 3-vessel disease 28%.	Mean 3.5 years.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Richardson, *et al.*, 1994 Australia	4.5% age ≥ 75, 0.7% age < 75, $p < 0.001$.	10.2%; 4-year survival: 0.84.		1.8% age ≥ 75, 1% age < 75.			17%; in-hospital and follow-up, 19%.	23 repeat procedures in follow-up.	High primary success rate achieved but frequent procedural difficulty. Incidence of CABG and acute MI low but 30-day mortality higher in ≥ 75 than < 75 age group. PTCA should be considered as option for treatment of elderly patients with severe angina.
Scott, *et al.*, 1994 USA	0% black, 1% white.	5-year death: 11% black, 10% white.	Free from angina 66% black, 81% white.	7% black, 5% white.	13% black, 14% white.		At follow-up: 20% black, 19% white.	25% black, 28% white.	Blacks have greater co-morbidity and coronary risk factors but same long-term outcome as whites. Results may be affected by small number of blacks in registry but reluctance to perform PTCA in blacks may be unfounded.
Weintraub, *et al.*, 1995b USA	1-vessel disease 0.2%, 2-vessel disease 0.4%, 3-vessel disease 1.2%, $p < 0.0001$.	Survival – 1-year: 1-vessel disease 99%, 2-vessel disease 97%, 3-vessel disease 95%. 5 years: 1-vessel disease 93%, 2-vessel disease 89%, 3-vessel disease 83%. 10 years: 1-vessel disease 86%, 2-vessel disease 76%. 9 years: 3-vessel disease 70% ($p < 0.0001$).	Angina: 1-vessel disease 30%, 2-vessel disease 28%, 3-vessel disease 33%, $p < 0.0001$.	1-vessel disease 0.8%, 2-vessel disease 0.9%, 3-vessel disease 0.2%, $p = 0.19$.	Free from MI at 1 year: 1-vessel disease 96%, 2-vessel disease 94%, 3-vessel disease 92%. At 5 years: 1-vessel disease 89%, 2-vessel disease 85%, 2-vessel disease 82%, $p < 0.0001$.		Free at 1 year: 1-vessel disease 92%, 2-vessel disease 89% 3-vessel disease 86%. At 5 years: 1-vessel disease 87%, 2-vessel disease 79%, 3-vessel disease 73%. At 10 years: 1-vessel disease 77%, 2-vessel disease 58%, $p < 0.0001$.	Free at 1 year: 1-vessel disease 80%, 2-vessel disease 77%, 2-vessel disease 73%. At 5 years: 1-vessel disease 69%, 2-vessel disease 61%, 3-vessel disease 61%. At 10 years: 1-vessel disease 58%, 2-vessel disease 45%. At 9 years: 3-vessel disease 46%. ($p < 0.0001$)	Number of vessels diseased correlates with in-hospital, long-term mortality, long-term MI and need for subsequent revascularisation. Angioplasty is infrequently used in 3-vessel disease.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Rozenman, *et al.*, 1995 Israel	Patients who underwent PTCA but not for MI or severe unstable angina. Cohort 2069 patients	Combined angiography and angioplasty or separate; combined (1719) vs. separate (350).	Male: 78% combined, 81% separate. Mean age, years: 59.7 combined, 58.8 separate. Multi-narrowing dilatation: 39% combined, 39% separate. Total or subtotal occlusions: 26% combined, 27% separate.	None.
Stein, *et al.*, 1995 USA	Diabetic patients undergoing PTCA. Cohort 10,433 patients	PTCA groups: diabetes (1133) vs. non-diabetes (9300).	Male: 62% diabetes, 75% non-diabetes, $p < 0.0001$. Mean age, years: 60 diabetes, 58 non-diabetes, $p < 0.0001$. 1-vessel disease: 68% diabetes, 72% non diabetes, $p = 0.004$. Diameter stenosis: 75% diabetes, 75% non-diabetes, $p = 0.08$. EF: 58% diabetes, 58% non-diabetes. Angina class III or IV: 67% diabetes, 61% non-diabetes, $p < 0.0001$. Multi-site PTCA: 22% diabetes, 23% non-diabetes.	Mean 4 years; 96% follow-up.
Malenka, 1996 USA (New England Cardio-vascular Disease Study Group)	Patients who underwent PTCA. Cohort, multicentre, prospective 12,232 patients	PTCA.	Males: 67.5%. Mean age, years: 61.1. 1-vessel disease, 61%; 2-vessel disease, 28%; 3-vessel disease, 11%. Left main disease: 2%. EF: 41–60%, 48%; > 60%, 40%. Previous PTCA, 26%; previous CABG, 10%. Diabetes: 21%. Angina: stable 23%, unstable 46%, post-MI 21%.	In-hospital only.
Altmann, *et al.*, 1996 USA	Patients who underwent PTCA. Cohort 2242 patients	Groups: before stents available (1525) vs. after stents available (717); NB: only 4% (27/717) actually received stents.	Males: before 70%, after 72%. Mean age, years: before 61, after 60. Previous PTCA: before 23%, after 23%. Previous CABG: before 11%, after 10%. Diabetes: before 16%, after 19%, $p < 0.05$. Unstable angina: before 61%, after 70%. Multi-vessel PTCA: before 7%, after 6%.	Mean 12.9 months.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Reste-nosis	CABG	Re-PTCA	Conclusions
Rozenman, *et al.*, 1995 Israel	0.7% combined, 1.1% separate.			1% combined, 1.1% separate.			0.5% combined, 0.3% separate.		Most patients who require angioplasty can be treated with combined angiography and angioplasty.
Stein, *et al.*, 1995 USA	0.4% diabetes, 0.3% non-diabetes.	5-year survival: 88% diabetes, 93% non-diabetes, $p < 0.0001$.		0.6% diabetes, 0.8% non-diabetes.	5-years freedom: 81% diabetes, 89% non-diabetes, $p < 0.0001$.		Follow-up: 23% diabetes, 14% non-diabetes, $p < 0.0001$.	43% diabetes, 32% non-diabetes, $p < 0.0001$.	Most appropriate management of patients with diabetes cannot be determined. PTCA offers low morbidity and mortality but high incidence of cardiovascular events.
Malenka, 1996 USA (New England Cardio-vascular Disease Study Group)	1-vessel disease: 0.4%. 2-vessel disease: 1.3%. 3-vessel disease: 3.4%. Total: 1%.			Death, CABG or MI 1-vessel disease: 4.5%. 2-vessel disease: 7.1%. 3-vessel disease: 9.3%. Total: 5.7%.			Death or emergent/ urgent CABG – 1-vessel disease: 3%. 2-vessel disease: 5.4%. 3-vessel disease: 7.3%. Total: 4.2%.		Practice and outcomes of PTCA in northern New England similar to reports from other regional registries but different from a registry of selected institutions. Concluded that PTCA, as performed in northern New England, safe and effective.
Altmann, *et al.*, 1996 USA	1.1% before, 0.7% after.		Of 27 who received stents: 81% no angina or CCS class I		Q wave: 0.5% before, 0.3% after.		Emergency: 2.9% before, 1.1% after, $p < 0.01$.	Of 27 who received stents: 2 (7%) had repeat PTCA.	Introduction of coronary stents for acute or threatened closure associated with > 50% reduction in PTCA complications overall and emergency bypass surgery, in particular, despite greater acuity of patients.

Health-related quality of life

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Englehart, 1993 Canada	Prospective cohort follow-up study.	40 adult patients who had undergone PTCA and were attending a routine angiography 6 months after the procedure. Inclusion criteria: ability to read English, no previous CABG, no physical problems on day of interview, consent.	83% male; mean age 57 years (males) and 65 years (females); 23/40 people had at least one chronic illness in addition to angina; 58% had previous MI; 83% had grade III or IV angina pre-PTCA, 10% post-PTCA.	6 months.
Gulanick & Naito, 1994 USA	Prospective cohort follow-up study. 54 patients	First time PTCA patients, 1990–91. Inclusion criteria: no previous PTCA, successful PTCA outcome, no complications needing surgery, age < 75 years, no co-morbidity that might impede recovery, telephone access, ability to complete questionnaire.	37/54 male; 31% stable, 28% unstable angina; 31 acute MI; 78% 1-vessel PTCA.	After PTCA: 1 week (100%), 6 weeks (87%), 12 weeks (78%).
McKenna, *et al.,* 1994 Australia	Assessment of series of patients admitted for PTCA surgery. Prospective series, single centre 209 patients	209 patients admitted for PTCA, with no major co-morbidity and no previous CABG.	76% male. Mean age (range), years: 56 (30–78). Functional class: I, 22%; II, 47%; III, 22%; IV, 9%. Previous MI: 34%. Angina duration (mean): 17 months. 1-vessel disease, 84%; > 1-vessel disease, 16%. Smoker: 48%. Hypertension: 45% Diabetes: 4%. Se cholesterol > 5.5 mmol/l: 66%. Obesity, 56%; sedentary, 68%.	6–8 weeks; 6–12 months (mean 11 months).

Study	Instruments used	Results	Conclusions
Englehart, 1993 Canada	SIP; SASS	Low SIP scores at 6 months follow-up against other (undefined) studies suggesting limited impact of angina on patients' HRQoL; data suggest condition has greater impact on psycho-social problems than physical ones. Poorer HRQoL on basis of SIP related to presence of additional chronic illness. SASS data suggest improved perception of health at 6 months compared with before PTCA. Positive perception of health increased with patients' age. Poorer health on basis of SIP related to perception of better health.	Patients have a good level of HRQoL after PTCA.
Gulanick & Naito, 1994 USA	Self-report of recovery for health status, expectations, risk behaviour. Tension and anxiety subscale of POMS for mood changes of intermediate duration.	Between 72% and 86% considered that they had achieved the expected benefits of PTCA. Low expectations of restenosis, low POMS score (low tension/anxiety).	Patients quite satisfied with results of PTCA, not overly anxious about restenosis.
McKenna, *et al.,* 1994 Australia	Functional capacity; total life satisfaction score (not validated); PGWB (from General Health Questionnaire).	209 patients had 311 lesions, leading to 91% successful dilatation. Mean % diameter stenosis reduced from 85% to 36%. PTCA primarily unsuccessful in 11 patients (5.3%). 19 patients re-PTCA, 14 patients CABG. Data on quality of life analysed on intention-to-treat basis (i.e. regardless of outcome of initial PTCA): (i) functional status: 86% patients no change at late follow-up; (ii) exercise time increased from 381 s to 560 s at 6–8 weeks, $p < 0.001$; (iii) total life satisfaction scores: median increased from 35 to 41 at 6–8 weeks, $p < 0.001$; (iv) PGWB scores improved from median of 30 to 14 at early follow-up, $p < 0.001$; (v) employment: 26% of 119 employed patients were working before PTCA, 79% at late follow-up; (vi) patient perception of PTCA: 58% very beneficial, 16% moderately beneficial, 7% slight benefit, 15% no benefit, 5% unsure of benefit.	Patient quality of life improves after PTCA and is sustained after 1 year.

Appendix 11

Summary tables of non-medical adjuncts to PTCA

Clinical effectiveness

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Topol, *et al.*, 1993b; Elliott, *et al.*, 1995 USA and Europe (CAVEAT)	Patients with diseased native coronary vessels, stenosis ≥ 60% and lesion length ≤ 12 mm. RCT, multicentre, double-blind 1012 patients	Groups: PTCA (500) vs. directional atherectomy (512).	Male: 75% atherectomy, 70% PTCA. Mean age, years: 59 atherectomy, 59 PTCA. 1-vessel disease: 66% atherectomy, 65% PTCA. Lesion length, mm: 8.9 atherectomy, 8.6 PTCA. Stenosis, %: 71 atherectomy, 73 PTCA. EF: 58% atherectomy, 56% PTCA. Diabetes: 19% atherectomy, 19% PTCA. Unstable angina: 66% atherectomy, 70% PTCA.	1 year; intention-to-treat.
Adelman, *et al.*, 1993 Canada (Canadian Coronary Atherectomy Trial)	Patients with angina or evidence of myocardial ischaemia, stenosis ≥ 60% in LAD artery suitable for either procedure. RCT, multicentre 274 patients	Groups: PTCA (136) vs. atherectomy (138).	Male: 80% atherectomy, 87% PTCA. Mean age, years: 57.7 atherectomy, 54.9 PTCA. Multi-vessel disease: 27% atherectomy, 20% PTCA. Lesion type A: 17% atherectomy, 13% PTCA. Lesion type B1: 43% atherectomy, 40% PTCA. Stenosis pre-procedure, %: 71 atherectomy, 70 PTCA. Stenosis post-procedure, %: 25 atherectomy, 33 PTCA. EF < 35%: 6% atherectomy, 5% PTCA. Diabetes: 17% atherectomy, 15% PTCA.	6 months; intention-to-treat.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Topol, *et al.*, 1993b; Elliott, *et al.*, 1995 USA and Europe (CAVEAT)	0% atherectomy, 0.4% PTCA.	6 months: 1.6% atherectomy, 0.6% PTCA. At 1 year: 2.2% atherectomy, 0.6% PTCA, $p = 0.035$.		19% atherectomy, 8% PTCA.	At 6 months: 8% atherectomy, 4% PTCA, $p = 0.04$. At 1 year: 9% atherectomy, 4% PTCA, $p = 0.005$.	At 6 months: 50% atherectomy, 57% PTCA, $p = 0.06$.	At 6 months: 8% atherectomy, 7% PTCA. At 1-year: 9% atherectomy, 9% PTCA.	At 6 months: 28% atherectomy, 30% PTCA. At 1-year: 25% atherectomy, 26% PTCA.	Although atherectomy led to greater initial gain in lumen size and a small reduction in restenosis rate, this was overshadowed by increase in adverse clinical outcomes and cost. Until techniques are improved or convincing, reproducible findings indicate certain subgroups benefit; angioplasty remains preferred option.
Adelman, *et al.*, 1993 Canada (Canadian Coronary Atherectomy Trial)	None.	0.7% atherectomy, 0% PTCA.	Class III or IV: 30% atherectomy, 20% PTCA.	4% atherectomy, 4% PTCA.	0% atherectomy, 1% PTCA.		5% atherectomy, 4% PTCA.	23% atherectomy, 22% PTCA.	Role of atherectomy remains undefined. However, compared with angioplasty, atherectomy did not result in better late outcomes in patients with lesions of proximal LAD coronary artery.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Fischman, *et al.*, 1994 USA (STRESS)	Patients with ischaemic heart disease, ≥ 70% stenosis, lesions ≤ 15 mm long, which could be spanned by single stent, and vessel diameter ≥ 3 mm. RCT, multicentre 410 patients	PTCA groups: standard balloon angioplasty (PTCA) (203) vs. Palmaz-Schatz stent (207).	Male: 83% stent, 73% PTCA, $p \leq 0.05$. 1-vessel disease: 64% stent, 68% PTCA. 2-vessel disease: 27% stent, 21% PTCA. 3-vessel disease: 9% stent, 11% PTCA. Mean age, years: 60 stent, 60 PTCA. EF: 61% stent, 61% PTCA. Lesion length, mm: 9.6 stent, 8.7 PTCA, $p < 0.001$. Stenosis: 75% stent, 75% PTCA. Diabetes: 15% stent, 16% PTCA. Hypertension: 43% stent, 45% PTCA. Unstable angina: 47% stent, 48% PTCA.	6 months; intention-to-treat except for 2 in stent group and 1 in PTCA group (excluded as did not meet entry criteria); 1 lost to follow-up.
Holmes, *et al.*, 1995 USA and Europe (CAVEAT II)	Patients with prior CABG and *de novo* vein graft lesions. RCT, multicentre 305 patients	Groups: PTCA (156) vs. directional atherectomy (149).	Male: 83% atherectomy, 85% PTCA. Mean age, years: 65 atherectomy, 65 PTCA. 1-lesion targeted: 89% atherectomy, 84% PTCA. 2-lesions targeted: 10% atherectomy, 15% PTCA. Lesion length, mm: 10.9 atherectomy, 11.0 PTCA. EF: 52% atherectomy, 50% PTCA. Diabetes: 36% atherectomy, 33% PTCA. Angina class III or IV: 80% atherectomy, 85% PTCA. Unstable angina: 89% atherectomy, 88% PTCA.	6 months; not really intention-to-treat analysis.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Fischman, *et al.*, 1994 USA (STRESS)	0% stent, 1.5% PTCA.	Late deaths: 1.5% stent, 0% PTCA.		Total: 5.4% stent, 5% PTCA.	Late MI: 1.5% stent, 2% PTCA.		Late CABG: 2.4% stent, 4.5% PTCA.	Late repeat PTCA: 9.8% stent, 11.4% PTCA.	Elective stent placement, compared with angioplasty has higher clinical success rate and reduces incidence of restenosis and need for subsequent revascularisation of treated lesion. If limitations of stent thrombosis and haemorrhagic complications can be overcome, implantation of Palmaz-Schatz stent may become preferred treatment in selected patients with new lesion in large coronary arteries.
Holmes, *et al.*, 1995 USA and Europe (CAVEAT II)	2% atherectomy, 2% PTCA.	Survival: 95% atherectomy, 92% PTCA.	Free from angina class > I: 66% atherectomy, 64% PTCA.	17% atherectomy, 11% PTCA.	Free from MI: 80% atherectomy, 84% PTCA.		Free from CABG: 94% atherectomy, 95% PTCA.	Free from revascularisation: 81% atherectomy, 72% PTCA, $p = 0.03$.	Directional atherectomy resulted in higher initial angiographic success rate and larger initial improvement in graft dimensions, but offset by initial increase in distal embolisation and non Q-wave MI. Trend towards decreased performance of repeated target vessel intervention at 6 months in atherectomy patients but no difference in restenosis rates.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Teirstein, *et al.*, 1997 USA	Patients underwent stenting as required and balloon dilation, then were randomised to catheter-based irradiation with iridium-192 (^{192}Ir) or placebo. 55 patients	Groups: ^{192}Ir (26) vs. placebo (29).	Mean age, years: 70 ^{192}Ir vs. 69 placebo. Male: 73% ^{192}Ir vs. 76% placebo. Diabetes: 27% ^{192}Ir vs. 41% placebo. Unstable angina: 42% ^{192}Ir vs. 55% placebo. Previous MI: 38% ^{192}Ir vs. 34% placebo. Elevated cholesterol: 54% ^{192}Ir vs. 59% placebo. Hypertension: 65% ^{192}Ir vs. 69% placebo. Previous restenoses: > 1: 52% ^{192}Ir vs. 55% placebo; > 2: 23% ^{192}Ir vs. 24% placebo. Number of stents in target lesion – 1: 38% ^{192}Ir vs. 45% placebo; – 2: 62% ^{192}Ir vs. 55% placebo. Left ventricular EF: 47% ^{192}Ir vs. 49% placebo. Location of target lesion – saphenous vein: 23% ^{192}Ir vs. 31% placebo; – LAD artery: 31% ^{192}Ir vs. 38% placebo; – ostial: 31% ^{192}Ir vs. 41% placebo; aorto-ostial: 12% ^{192}Ir vs. 17% placebo. Lesion length, mm: 13 ^{192}Ir vs. 12 placebo; Length > 10 mm: 58% ^{192}Ir vs. 45% placebo.	6 months.
Macaya, *et al.*, 1996 Europe (Benestent trial) (also Serruys, *et al.*, 1994)	Patients with stable angina and single new lesion, aged ≥ 30 and ≤ 75 years. RCT, clinical evaluation, blind 516 patients	Groups: PTCA (258) vs. Palmaz-Schatz stent (262).	Male: 82% PTCA, 80% stent. Mean age, years: 58 PTCA, 57 stent. Prior CABG: 2% PTCA, 0% stent. Prior PTCA: 3% PTCA, 2% stent. Concentric lesion: 46% PTCA, 50% stent. Length of lesion, mm: 6.96 PTCA, 7.06 stent. Diabetes: 6% PTCA, 7% stent. Angina class III or IV: 59% PTCA, 54% stent.	7 months and 1 year.
Schomig, *et al.*, 1996 Germany	Patients who had successful implantation of intracoronary stents after PTCA. RCT 517 patients	Groups: antiplatelet therapy (250 mg ticlopidine b.d.) (257) vs. anticoagulant therapy (phenprocoumon) (260).	Males: 77% antiplatelet, 77% anticoagulant. Multi-vessel disease: 77% antiplatelet, 70% anticoagulant. Previous CABG: 7.8% antiplatelet, 13% anticoagulant. Previous PTCA: 18% antiplatelet, 21% anticoagulant. Diabetes: 16% antiplatelet, 20% anticoagulant. Acute MI: 24% antiplatelet, 24% anticoagulant. Unstable angina: 46% antiplatelet, 43% anticoagulant.	30 days; 24 anticoagulant group stopped therapy, 4 antiplatelet group stopped therapy.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Teirstein, *et al.*, 1997 USA				One on day 18 in ^{192}Ir group caused by stent thrombosis in patient non-compliant with ticlopidine regimen.		Restenosis of stent: 8% vs. 36%, $p = 0.02$. Stent and border: 17% vs. 54%, $p = 0.01$.	None.		No initial differences in luminal diameter. No major bleeding complications in either group.
Macaya, *et al.*, 1996 Europe (Bene-stent trial)	None.	At 1 year: 0.8% PTCA, 0.8% stent.	Class III or IV: 3% PTCA, 2% stent.	0.8% PTCA, 1.9% stent.	1.9% PTCA, 3.5% stent.		Emergency: 1.6% PTCA, 1.9% stent. Elective: 3.5% PTCA, 5% stent.	21% PTCA, 10% stent.	Elective native coronary artery stenting in patients with stable angina maintained to at least 1 year after procedure; results significantly reduced requirement for repeat intervention.
Schomig, *et al.*, 1996 Germany	At 1 month: 0.4% antiplatelet, 0.8% anticoagulant.			At 1 month: nonfatal 0.8% antiplatelet, 3.5% anticoagulant, $p = 0.06$.			At 1 month: 0 antiplatelet, 0.4% anticoagulant.	At 1 month: 1.2% antiplatelet, 5% anticoagulant, $p = 0.02$.	Results indicate risk–benefit ratio for stenting may be substantially improved by use of combined antiplatelet therapy.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Sirnes, *et al.*, 1996 Norway and Sweden (SICCO)	Patients aged > 18 years who had PTCA of occluded coronary artery (randomised from 3080 PTCAs, of which 590 successful). RCT, multicentre; 119 patients	Groups: PTCA only (59) vs. PTCA + stent (58).	Males: 20% PTCA, 16% stent. Diseased vessels: 1.5 PTCA, 1.5 stent. 1-vessel disease: 62%. EF: 63% PTCA, 63% stent. CCS class I/II: 24% PTCA, 22% stent.	6 months; two from each group had no follow-up angiography.
Versaci, *et al.*, 1997 Italy	Patients with angina, MI or both, randomised to stents or PTCA. 120 patients	PTCA (n = 60) vs. stents (n = 60).	Mean age, years: 57 PTCA vs. 58 stent. Males: 83% PTCA vs. 92% stent. Previous MI: 25% PTCA vs. 28% stent. Angina class I: 8% PTCA vs. 7% stent; II: 45% PTCA vs. 37% stent; III: 18% PTCA vs. 30% stent; V: 10% PTCA vs. 10% stent. Mean EF: 54% PTCA vs. 5% stent.	12 months.
Cohen, *et al.*, 1997 Canada	Randomised comparison of atherectomy with balloon angioplasty. 214 patients initially randomised	Atherectomy vs. directional atherectomy.	All patients with *de novo* lesions in the proximal one-third of the LAD artery.	Median of 18 months after randomisation.
Appelman, *et al.*, 1996 The Netherlands	Patients with stable angina and lesions > 10 mm suitable for PTCA. RCT, multicentre 308 patients	PTCA groups: excimer laser angioplasty (151) vs. balloon angioplasty (157).	Male: 76% laser, 73% balloon. 1-vessel disease: 55% laser, 50% balloon. Lesion length > 20 mm: 22% laser, 28% balloon. Type B lesion: 55% laser, 46% balloon. Type C lesion: 49% laser, 60% balloon. Mean age, years: 58 laser, 59 balloon. Prior CABG: 7% laser, 8% balloon. Prior PTCA: 11% laser, 16% balloon. Diabetes: 10% laser, 13% balloon. Angina class III or IV: 64% both groups.	6 months; 98% complete follow-up.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Sirnes, *et al.*, 1996 Norway and Sweden (SICCO)	None.	None.	Free from angina: 24% PTCA, 57% stent, $p < 0.001$.	1 in stent group.	None.	74% PTCA, 32% stent, $p < 0.001$.	At 6 months: 1.7% PTCA, 3.4% stent. At 300 days: 1.7% PTCA, 5.2% stent.	At 6 months: 3.4% PTCA, 1.7% stent. At 300 days: 41% PTCA, 17% stent.	This study shows for first time in an RCT that long-term results after PTCA of chronic coronary occlusion are substantially improved by intracoronary stents. When technically feasible, stenting is recommended in all successfully recanalised chronic coronary occlusions.
Versaci, *et al.*, 1997 Italy		One in each group from cardiac causes.	PTCA 25% vs. 10% stenting, $p = 0.05$.	Bleeding and vascular complications more common with stents, $p = 0.12$.	Nonfatal: 3% vs. 2%.	40% PTCA vs. 19% stenting, $p = 0.02$.			Authors suggest that in symptomatic patients with isolated stenosis of proximal LAD coronary artery, primary stenting has more favourable 12-month clinical outcome than PTCA and lower restenosis rates.
Cohen, *et al.*, 1997 Canada		1.5% atherectomy vs. 2.2% balloon angioplasty.	Persistent class III/IV not treated by reintervention: 1.5% vs. 2.2%.	5.1% vs. 5.9%.			13.1% atherectomy vs. 12.6% balloon angioplasty.		No group differences in adverse events. Choice of treatment has no impact on clinical outcome over this period.
Appelman, *et al.*, 1996 The Netherlands	None.	None.	No angina: 60% laser, 60% balloon.	1.3% laser, 1.3% balloon.	1.3% laser, 0.6% balloon.		In-hospital and follow-up: 11% laser, 11% balloon.	In-hospital and follow-up: 21% laser, 18% balloon.	Results of this trial demonstrate no additional benefit of excimer laser over balloon angioplasty with current laser techniques.

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Reifart, *et al.*, 1997 Germany	Patients warranting elective percutaneous revascularisation for complex lesion randomised to either ballon angioplasty, excimer laser angioplasty or rotational atherectomy. 685 patients	Group 1, balloon angioplasty (n = 222), vs. Group 2, excimer laser angioplasty (n = 232), vs. Group 3, rotational atherectomy (231).	Mean age, years: Group 1, 63; 2, 62; 3, 62. Male: Group 1, 81%; 2, 78%; 3, 80%. Diabetes: Group 1, 16%; 2, 17%; 3, 15%. Unstable angina: Group 1, 12; 2, 16, 3, 18. Asymptomatic: Group 1, 16; 2, 17; 3, 17. Previous MI: Group 1, 45;2, 42; 3, 47. Previous bypass: Group 1, 6; 2, 8; 3, 6. 1-vessel disease: Group 1, 48%; 2,, 47%; 3, 42%. 2-vessel disease: Group 1, 41%; 2, 41%; 3, 41%. 3-vessel disease: Group 1, 11%; 2, 11%; 3, 18%. Left ventricular score > 10: Group 1, 5; 2, 5; 3, 6. Location of lesion – LAD artery: Group 1, 48%; 2, 52%; 3, 51%. Left circumflex artery: Group 1, 24%; 2, 19%; 3, 20%. Right coronary artery: Group 1, 27%; 2, 26%; 3, 28%. Left main disease: Group 1, 2,3, 0%. Bypass graft: Group 1, 1%; 2, 3%; 3, 1%.	6 months.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Reifart, *et al.*, 1997 Germany	Composite endpoint (mortality, CABG or Q-wave MI): Group 1, 3%; 2, 4%; 3, 3% (NS).	Composite endpoint (mortality, CABG, repeated angioplasty or Q-wave MI): Group 1, 37%; 2, 48%; 3, 46%; p = 0.06.	Class I: Group 1, 64%; 2, 62%; 3, 63%; NS.			Group 1, 47%; 2, 59%; 3, 57%; p = 0.14.			Study unblinded. Authors suggest further evaluation warranted.

Health-related quality of life

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Karrillon, *et al.*, 1996 France	Patients who underwent successful stenting procedures. Multicentre, prospective, cohort 2900 patients	PTCA plus stents.	Males: 84%. Mean age, years: 61.1; age ≥ 75 years: 93%. Restenosis: 6.7%. Post-CABG angina: 34%; unstable angina/acute MI: 57%; stable angina/elective PTCA/restenosis: 43%.	1 month.
Hall, *et al.*, 1996 Japan	Patients with proven coronary artery disease. RCT 223 patients	Groups: 250 mg ticlopidine b.d. + 325 mg/day aspirin (123) vs. 325 mg/day aspirin (103).	Males: 89% aspirin, 88% ticlopidine. 1-vessel disease: 59% aspirin, 59% ticlopidine. 2-vessel disease: 29% aspirin, 31% ticlopidine. 3-vessel disease: 12% aspirin, 10% ticlopidine. Mean age, years: 58 aspirin, 57 ticlopidine. EF: 58% aspirin, 59% ticlopidine. Previous PTCA: 10% aspirin, 10% ticlopidine. Previous CABG: 3% aspirin, 11% ticlopidine, p = 0.02. Diabetes: 6% aspirin, 16% ticlopidine, p = 0.01. CCS class III or IV: 44% aspirin, 42% ticlopidine.	1 month; three (2.4%) withdrew from ticlopidine treatment because of side-effects. No withdrawals in aspirin only group.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Karrillon, *et al.*, 1996 France	At 1 month: 17 (0.6%).			At 1 month: 44 (1.5%).			At 1 month: 10 (0.3%).	At 1 month: 13 (0.5%).	Stent-related cardiac events remain very low.
Hall, *et al.*, 1996 Japan	At 1 month: 2.9% aspirin, 0% ticlopidine.			At 1 month: 3.9% aspirin, 0.8% ticlopidine.			At 1 month: none (emergency or elective).	At 1 month: 1.9% aspirin, 0.8% ticlopidine.	Results of study provide further evidence of safety of treatment with only antiplatelet therapy after optimal stent expansion.

Cost and cost-effectiveness (primary data)

Study	Design	Baseline characteristics	Selection criteria	Methods
Dick, *et al.*, 1991 USA	Prospective, single centre, cost analysis of cohort of patients who received angioplasty (n = 50), directional atherectomy (n = 72) or coronary stenting (n = 27). Not randomised	Male: PTCA 66%, atherectomy 78%, stent 24%. Mean age, years: PTCA 60, atherectomy 58, stent 58. Previous MI: PTCA 34%, atherectomy 38%, stent 63%. Previous CABG: PTCA 22%, atherectomy 18%, stent 30%. Previous PTCA: PTCA 24%, atherectomy 31%, stent 93%. > 1-vessel disease: PTCA 40%, atherectomy 39%, stent 48%.	Elective patients with NYHA class II/III angina. 858 PTCA patients (50 randomly selected for costing); 112 atherectomy patients (72 included) 40 stent patients (27 included). Patients excluded for: acute MI, cardiogenic shock or unstable angina.	Perspective: partial health service (hospital); sample of patients included. Based on hospital charges, converted to costs using cost-to-charge ratio (0.76); includes hospital fees, excludes clinician fees. Expressed in 1989 US$, sources not reported.
Topol, *et al.*, 1993a USA and Europe	Prospective, multicentre (35 centres) cost analysis, attached to an RCT, of the in-hospital costs of conventional PTCA vs. directional atherectomy.	PTCA: n = 500, 297 included in cost data. Atherectomy: n = 512, 308 included in cost data. See page 143	Symptomatic IHD, no previous cardiac intervention, > 60% stenosis, > 12 mm lesion.	Perspective: partial health service (hospital); patients included: all? (not clear). Based on hospital charges; includes hospital charges but no details of exclusions. Expressed in US$ but year and source of costs not reported.
Guzman, *et al.*, 1994 USA	Retrospective, single centre, case-control cost analysis of in-hospital costs of conventional PTCA vs. atherectomy. Not randomised	Male: PTCA 75%, atherectomy 75%. Mean age (SD), years: PTCA 60 (9.8), atherectomy 59.7 (10). Previous PTCA: PTCA 28%, atherectomy 43%. Previous CABG: PTCA 38%, atherectomy 36%. Previous MI: PTCA 27%, atherectomy 43%. Multi-vessel disease: PTCA 30%, atherectomy 31%.	126 consecutive patients who underwent atherectomy for 1-vessel, 1-lesion angina (rotational 44, TEC 17, directional 65). Control group: 126 patients matched by age and gender who underwent PTCA.	Perspective: partial health service (hospital); all patients included. Based on hospital charges, cost-to-charge ratios used; includes hospital charges but excludes diagnostic cardiac catheterisation, physician fees. Expressed in US$; sources reported.

Study	Follow-up (duration of costing)	Results	Conclusions
Dick, *et al.*, 1991 USA	Initial admission only.	Mean hospitalisation period, days (SD): PTCA 1.5 (1.3), atherectomy 2.2 (3.9), stent 4.9 (2.4). Catheter laboratory plus device costs: PTCA $4044, atherectomy $4666, stent $6668. Total hospital costs: PTCA $6220, atherectomy $8329, stent $12,574. % costs ratio: PTCA 100%, atherectomy 134%, stent 203%, $p < 0.001$.	103% and 34% increase in hospital charges associated with stenting and directional atherectomy, respectively, compared with PTCA. This chiefly due to prolonged length of hospitalisation, device costs, laboratory fees, and, in patients with stents, prolonged times needed to achieve systemic anticoagulation. (NB: are these groups at all comparable?)
Topol, *et al.*, 1993a USA and Europe	6 months.	Hospitalisation period, days: atherectomy 5.7, PTCA 5.8. Total costs: atherectomy $11,904, PTCA $10,637, $p = 0.006$. Total charges: atherectomy $17,489, PTCA $15,263, $p = 0.004$.	Atherectomy associated with higher initial hospital costs and charges than conventional PTCA (NB: hospital costs taken from 19 unspecified centres, 605 patients, basis for selection not specified). Derivation of 'costs' and 'charges' not detailed.
Guzman, *et al.*, 1994 USA	Hospital stay.	Mean length of hospitalisation (SD), days: atherectomy 3.7 (5.2), PTCA 3.5 (3.7), not significant. Mean number catheters used (SD): atherectomy 2.4/1; PTCA 1.3/0.6, $p < 0.0001$. Overall cost-to-charge ratio: 0.72 (SD = 0.10). Mean total costs: atherectomy: $9345/8856, PTCA: $7301/4637 ($p < 0.02$).	Atherectomy devices appear to be 30% more expensive than conventional balloon angioplasty (and associated with a lower success rate). This difference was found to be principally related to increases in the cost of supplies.

continued

Cost and cost-effectiveness (primary data) *contd*

Study	Design	Baseline characteristics	Selection criteria	Methods
Cohen, *et al.*, 1995 USA	Prospective multicentre (8 of 13 centres in RCT) cost analysis of conventional PTCA compared with coronary stenting, attached to the STRESS RCT.	PTCA, n = 105; stent, n = 102. See appendix 11 49 patients declined to be in the economic sub-study.	see page 144.	Perspective: partial health service (hospital). Sample of patients included. Based on bottom-up costs for resources used during procedure, topdown for other hospital costs. Includes hospital costs, physician fees. Exclusions: not detailed. Expressed in US$ 1994, sources of costs reported.
Goods, *et al.*, 1996 USA	Prospective, single-centre cost analysis of the impact of not using warfarin post-stenting. Consecutive series of patients, all having aspirin and ticlodipine.	Warfarin: n = 33; no warfarin: n = 33. Male: warfarin 79%, no warfarin 64%. 1-, 2-, 3-vessel disease: warfarin 36, 45, 19; no warfarin 39, 30, 31. Mean age (SD), years: warfarin 55 (10); no warfarin 60 (11).	Elective.	Perspective: partial health service (hospital); all patients included. Based on hospital costs derived from cost-to-charge ratios; includes procedural and non-procedural costs. Expressed in US$; sources of costs not reported.

Study	Follow-up (duration of costing)	Results	Conclusions
Cohen, *et al.*, 1995 USA	1 year from procedure.	Mean initial procedure costs (SD), $: PTCA 3505 (1505), stent 4691 (1156), $p < 0.001$. Mean hospitalisation (SD), days: PTCA 4.8 (3.6), stent 7.5 (3.4), $p < 0.001$. Mean initial hospital costs (SD), $: PTCA 7505 (5015), stent 9738 (3248), $p < 0.0001$. Mean repeat hospitalisation costs (SD), $: PTCA 3359 (7100), stent 1918 (4841), NS. Mean 1-year costs (SD), $: PTCA 10,865 (9073), stent 11,656 (5674), $p < 0.001$.	Among patients randomised to initial stenting, major vascular complications associated with increased postoperative length of stay and increased initial hospital costs. Even in patients with no vascular complications, stenting was associated with significantly higher 1-year treatment cost than conventional angioplasty.
Goods, *et al.*, 1996 USA	Hospital stay.	Mean initial hospitalisation, days: warfarin 5.9, no warfarin 2.1, $p < 0.0001$. Mean procedural costs, $: warfarin 5642, no warfarin 5426, NS. Mean non-procedural costs, $: warfarin 6647, no warfarin 2803, $p < 0.0001$.	Use of aspirin and ticlodipine after stenting without warfarin allowed for early discharge. Total hospitalisation costs reduced by 33% and non-procedural costs reduced by 58%.

Cost and cost-effectiveness (models)

Study (per-spective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusions
Cohen, *et al.,* 1994 USA (Third party payer) See also updated model: Cohen & Baim, 1995	To examine relative cost-effectiveness of conventional PTCA, primary stenting and secondary stenting in symptomatic 1-vessel coronary disease; (CUA).	Theoretical 55-year-old man with symptomatic 1-vessel disease. (i) decision analytic model (ii) Markov post-revascularisation model (iii) Assumptions tested using sensitivity analysis.	Clinical: literature review to 1993 – RCTs and other 'quality checked' data. QALYs from Pliskin, *et al.,* 1981. Economic: CABG, PTCA, stent costs from Cohen, *et al.,* 1993 (costs in 1991 US$).	Lifetime of patient cohort.	QALYs: PTCA 19.24, stent 19.28, secondary stent 19.25. Lifetime costs, $: PTCA 52,100, stent 52,700, secondary stent 52,400. Incremental cost per QALY (compared with PTCA), $: stent 23,600, secondary stent 72,500.	Major determinants of cost-effectiveness of stenting are relative restenosis rates and incremental costs of stenting. Stenting may be a reasonably cost-effective initial treatment for patients with symptomatic 1-vessel disease. Secondary stenting less effective and less cost-effective than primary stenting over wide range of plausible assumptions.
Cohen, & Baim, 1995 USA (Third party payer) See also earlier model: Cohen, *et al.,* 1994.	To examine relative cost-effectiveness of conventional PTCA, primary stenting and secondary stenting in symptomatic 1-vessel coronary disease; (CUA)	Theoretical 55-year-old man with symptomatic 1-vessel disease. (i) decision analytic model (ii) Markov post-revascularisation model (iii) Assumptions tested using sensitivity analysis.	Clinical: literature review to 1994 – RCTs and other 'quality checked' data, including that from Benestent and STRESS trials. QALYs from Pliskin, *et al.,* 1981. Economic: CABG, PTCA, stent costs from Cohen, *et al.,* 1993 (costs in 1991 US$).	Lifetime of patient cohort.	QALYs: PTCA 19.24, stent 19.28, secondary stent 19.25. Lifetime costs, $: PTCA 52,100, stent 52,700, secondary stent 52,400. Life-years and costs discounted at 5% p.a. Incremental cost per QALY (compared with PTCA), $: stent 33,700, secondary stent 72,500. Sensitivity analysis: PTCA restenosis rate reduction increases incremental cost per QALY for stenting.	Major determinants of cost-effectiveness of stenting are relative restenosis rates and incremental costs of stenting. Stenting may be reasonably cost-effective initial treatment for patients with symptomatic 1-vessel disease. Secondary stenting is less effective and less cost-effective than primary stenting.

Appendix 12

Summary tables of medical adjuncts to PTCA

Clinical effectiveness

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Thornton, *et al.*, 1984 USA	Successful PTCA procedure without complications. RCT 248 patients	Groups: coumadin (122) vs. aspirin, 325 mg (126).	Male: 81% coumadin, 79% aspirin. Diameter stenosis: 73% coumadin, 69% aspirin. Mean age, years: 53 coumadin, 53 aspirin.	9 months; 95% coumadin, 89% aspirin.
Corcos, *et al.*, 1985 USA	Patients who had successful PTCA. RCT 92 patients	Groups: diltiazem 270 mg/day (46), placebo (46).	Male: 78% diltiazem, 76% placebo. Mean age, years: 51 diltiazem, 50 placebo. 1-vessel disease: 85% diltiazem, 85% placebo. EF: 65% diltiazem, 63% placebo. Stenosis pre-PTCA: 79% diltiazem, 77% placebo. Stenosis post-PTCA: 38% diltiazem, 37% placebo. Prior CABG: 4% diltiazem, 7% placebo. Prior PTCA: 7% diltiazem, 4% placebo. Diabetes: 9% diltiazem, 9% placebo. Angina class III: 41% diltiazem, 52% placebo. Angina class IV or unstable: 28% diltiazem, 13% placebo.	Mean 8 ± 5 months.
Stone, *et al.*, 1989 USA	Patients undergoing 2nd, 3rd or 4th PTCA of same coronary segment. Not those with unstable angina, acute MI, insulin-dependent diabetes or peptic ulcers. RCT 102 patients	Groups: steroid regimen (52) – methylprednisolone, 125 mg i.m. evening before and morning of PTCA, plus prednisolone, 60 mg q.d.s. for 7 days, or controls (50). Standard medical regimen taken for 2 months by all patients.	Male: 83%. 1-vessel disease: 32%. Mean age, years: 56. No differences with respect to age, gender, angina duration, number of prior PTCA procedures, distribution of stenoses dilated. 1–5 lesions dilated per patient; mean, 2.1 steroid group, 2.0 control group.	Minimum 8 months.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Thornton, *et al.*, 1984 USA			36% coumadin, 27% aspirin.						Coumadin therapy does not appear any more advantageous than aspirin in prevention of restenosis after PTCA. Because coumadin has numerous side-effects, it is not the preferred therapy after PTCA.
Corcos, *et al.*, 1985 USA						1-vessel disease: 14% diltiazem, 18% placebo. Multi-vessel disease: 50% (1/2) diltiazem, 43% (3/7) placebo.			Study only of small number of patients, results need to be confirmed by large, multicentre trials. However, they provide evidence against role of coronary spasm in producing restenosis in patients with fixed coronary stenoses undergoing PTCA.
Stone, *et al.*, 1989 USA		8% steroids, 2% controls, p = NS.	Class III/IV: 20% steroids, 39% controls, p = NS.		0% steroids, 2% controls, p = NS.	No evidence of restenosis: 58% steroids, 52% controls.			In this trial, short courses of high-dose corticosteroids, though without toxicity, were not found to decrease frequency of restenosis following PTCA.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Nye, *et al.*, 1990 New Zealand	Patients who received PTCA procedure. RCT, double-blind (?) 108 patients	PTCA groups: aspirin + dipyridamole (35); eicosapentaenoic acid (EPA) (36), and placebo (37).	Male: 66% aspirin, 78% EPA, 76% placebo. Mean age, years, males: 53 aspirin, 53 EPA, 55 placebo. Mean age, years, females: 56 aspirin, 59 EPA, 55 placebo.	≤ 1 year; 93% restudied.
O'Keefe, *et al.*, 1991 USA	Patients having PTCA, not for acute MI and without severe concomitant illness. RCT, double-blind 201 patients	Groups: diltiazem (102), placebo (99). Diltiazem dose ranged from 240 mg to 360 mg per day, taken for 12 months.	Male: 86% diltiazem, 82% placebo. Area stenosis pre-PTCA: 85% diltiazem, 85% placebo. Area stenosis post-PTCA: 52% diltiazem, 48% placebo. Diabetes: 6% diltiazem, 9% placebo. Smoking: 72% diltiazem, 80% placebo. Peripheral vascular disease: 3% diltiazem, 3% placebo.	12 months; 60% angiographic follow-up.
MERCATOR Study Group, 1992 Europe	Patients who had successful, uncomplicated PTCA. 27% (478/1755) of those screened were enrolled in study. RCT, multicentre, double-blind 693 patients	Groups: cilazapril, 5 mg (341), placebo (352), taken for 6 months.	Male: 83% placebo, 83% cilazapril. Mean age, years: 56 placebo, 57 cilazapril. 1-vessel disease: 65% placebo, 66% cilazapril. 1-site PTCA: 82% placebo, 82% cilazapril. Prior CABG: 1.7% placebo, 2.1% cilazapril. Prior PTCA: 1.7% placebo, 1.1% cilazapril. Diabetes: 6% placebo, 6% cilazapril. Angina class III or IV: 48% placebo, 46% cilazapril.	6 months; intention-to-treat analysis.
Darius, *et al.*, 1992 Germany	Patients referred for PTCA of coronary artery stenoses. RCT, double-blind 32 patients	PTCA groups: ciprostene (infusion rate 40 ng/kg/min intracoronarily before and 120 ng/kg/min i.v. after) (17) or placebo (15).	Male: 78%. Mean age, years: 52.8. Stenosis: 83% ciprostene, 81% placebo. Stable angina: 6 (35%) ciprostene, 5 (33%) placebo. Unstable angina: 6 (35%) ciprostene, 7 (47%) placebo.	6 months; five in ciprostene group and three in placebo group lost to follow-up.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Nye, *et al.*, 1990 New Zealand			No angina: 62% aspirin, 75% EPA, 57% placebo.			17% aspirin, 11% EPA, $p < 0.05$ vs. placebo, 30% placebo.			EPA can be used as alternative to aspirin/dipyridamole in post-PTCA patients. Further study required to determine potential on post-CABG patients.
O'Keefe, *et al.*, 1991 USA	1% diltiazem, 1% placebo.	3% diltiazem, 0% placebo.	37% diltiazem, 39% placebo.	0% diltiazem, 3% placebo.	0% diltiazem, 1% placebo.	36% diltiazem, 32% placebo.	1% diltiazem, 1% placebo.		Diltiazem did not influence overall restenosis rate or prevent late events after coronary angioplasty.
MERCATOR Study Group, 1992 Europe		< 1% placebo, < 1% cilazapril.	19% placebo, 20% cilazapril.		2.3% placebo, 1.4% cilazapril.			Revascularisation: 14% placebo, 15% cilazapril.	Long-term ACE inhibition with cilazapril, 5 mg b.i.d., does not prevent restenosis and does not favourably influence overall outcome after PTCA.
Darius, *et al.*, 1992 Germany						Stenosis at 6 months: 55% ciprostene, 63% placebo.	Within 48 hours: one in placebo group.		In this study with limited number of 32 patients, angiographic analyses of coronary artery stenoses hints of possible beneficial effect of ciprostene in patients with unstable angina. Thus, further studies involving larger cohort of patients needed.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Faxon, *et al.*, 1994 USA	Patients aged ≥ 21 years, who had first successful PTCA at present site. RCT, multicentre 458 patients	Groups: placebo (231), enoxaparin (heparin) 40 mg/day s.c. (227), taken for 28 days.	Male: 82% placebo, 83% enoxaparin. Mean age, years: 57 placebo, 58 enoxaparin. 1-vessel disease: 50% placebo, 48% enoxaparin. 1-lesion PTCA: 69% placebo, 78% enoxaparin. Lesion type A: 40% placebo, 40% enoxaparin. Lesion type B: 56% placebo, 54% enoxaparin. Stenosis: 71% placebo, 72% enoxaparin. EF: 59% placebo, 60% enoxaparin. Angina class III/IV: 46% placebo, 50% enoxaparin.	24 weeks (and 1 and 4 weeks); intention-to-treat analysis. Per protocol: 22% placebo, 19% enoxaparin excluded.
EPIC investi-gators, 1994 USA	Patients with acute MI, unstable angina or proven high risk. RCT, multicentre, double-blind 2099 patients	Groups: placebo (696), c7E3 Fab bolus plus placebo infusion (B) (695), or c7E3 Fab bolus plus infusion (B + I) (708).	Male:73% placebo, 72% B, 71% B + I. 1-vessel disease: 54% placebo, 51% B, 55% B + I. 2-vessel disease: 29% placebo, 34% B, 31% B + I. 3-vessel disease: 17% placebo, 15% B, 14% B + I. Mean age, years: 61 placebo, 60 B, 62 B + I. Previous PTCA: 25% placebo, 20% B, 22% B + I. Previous CABG: 15% placebo, 14% B, 16% B + I. Diabetes: 26% placebo, 23% B, 23% B + I.	In-hospital only; intention-to-treat basis.
Gerschlick, *et al.*, 1994 UK	Patients undergoing PTCA but not for total coronary occlusion, vein graft lesions or after previous PTCA. RCT, double-blind 155 patients	Groups: epoprostenol (prostacyclin PGI_2) (76), placebo (79); taken for 36 hours after PTCA.	Male: 82% PGI_2, 88% placebo. Mean age, years: 56 PGI_2, 53 placebo. Single PTCA: 82% PGI_2, 81% placebo. Stenotic diameter pre-PTCA: 0.64 mm PGI_2, 0.63 mm placebo. Stenotic diameter post-PTCA: 2.5 mm PGI_2, 2.2 mm placebo. Diabetes: 3% PGI_2, 1% placebo. Stable angina: 58% PGI_2, 54% placebo. Angina class III/IV: 69% PGI_2, 66% placebo.	6 months.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Faxon, *et al.*, 1994 USA		0.4% placebo, 0.4% enoxaparin.	17% placebo, 16% enoxaparin.		2% placebo, 2% enoxaparin.	No evidence of restenosis: 40% placebo, 40% enoxaparin.			Although study demonstrates no effect on prevention of restenosis, further study warranted. High-dose, local delivery or combination therapy with other agents may be needed to inhibit this complex process.
EPIC investi-gators, 1994 USA	1.7% placebo, 1.3% B, 1.7% B + I			8.6% placebo, 6.2% B, 5.2% B + I; $p = 0.013$.			3.6% placebo, 2.3% B, 2.4% B + I.	4.5% placebo, 3.6% B, 0.8% B + I.	Trial demonstrates beneficial effect of substantial and sustained blockade of glycoprotein IIb/IIIa receptor in patients undergoing high-risk PTCA but at risk of increased bleeding.
Gerschlick, *et al.*, 1994 UK		0% PGI_2, 4% placebo.	Grade 3 or 4: 4% PGI_2, 0% placebo. Admitted for angina: 22% PGI_2, 12% placebo.			29% PGI_2, 38% placebo.			Trial set up to detect 50% reduction; this could be reason why lesser benefit could not be demonstrated. However, other aspects of study suggest that PGI_2 in doses infused did not significantly alter basic biological process.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Onaka, *et al.*, 1994 Japan	Patients who had successful, elective PTCA. RCT (randomised by birthdays) 66 patients	Groups: pravastin 5 mg or 10 mg (29), controls (37); taken for 4 months.	Male: 62% pravastin, 59% controls. Mean age, years: 59 pravastin, 60 controls. 1-vessel disease: 79% pravastin, 81% controls. Stenosis pre-PTCA: 90% pravastin, 89% controls. Stenosis post-PTCA: 37% pravastin, 43% controls. Obstruction diameter pre-PTCA: 0.6 mm pravastin, 0.7 mm controls. Obstruction diameter post-PTCA: 2.1 mm pravastin, 2.1 mm controls. Prior CABG: 3% pravastin, 0% controls. Diabetes: 30% pravastin, 30% controls.	4 months.
Hoberg, *et al.*, 1994 Germany	High-risk patients who had initially successful PTCA but not acute MI, > 70 years old, previous revascularisation or severe concomitant disease. RCT, double-blind 196 patients	Groups: placebo (98), verapamil 240 mg/day (98); taken for 6 months.	Male: 79% verapamil, 85% placebo. Mean age, years: 55 verapamil, 55 placebo. Multi-vessel disease: 37% verapamil, 42% placebo. Stenosis pre-PTCA: 86% verapamil, 86% placebo. Stenosis post-PTCA: 34% verapamil, 35% placebo. Diabetes: 14% verapamil, 4% placebo. Stable angina: 58% verapamil, 57% placebo.	6 months; 91% verapamil and 85% placebo group had angiography. 13% verapamil and 11% placebo excluded for non-compliance.
Faxon, 1995 USA and Canada (MARCATOR study group)	Patients scheduled for first PTCA with no concomitant disease. RCT, multicentre, double-blind 1436 from 16,097 PTCA procedures enrolled in study (9%).	Groups: placebo (361), 1 mg cilazapril (359), 5 mg cilazapril (361), 10 mg cilazapril (355); taken for 6 months.	Male: 83% placebo, 82% 1 mg, 81% 5 mg, 75% 10 mg. Mean age, years: 57 placebo, 58 1 mg, 58 5 mg, 58 10 mg. Multi-dilatation: 23% placebo, 21% 1 mg, 22% 5 mg, 23% 10 mg. Diabetes: 12% placebo, 10% 1 mg,16% 5 mg, 18% 10 mg. Angina class III/IV: 59% placebo, 56% 1 mg, 55% 5 mg, 57% 10 mg. Current smoker: 21% placebo, 23% 1 mg, 19% 5 mg, 19% 10 mg.	6 months; intention-to-treat analysis. 75% in per protocol analysis.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Onaka, *et al.*, 1994 Japan		None.	Recurrence of symptoms: 24% pravastin, 27% controls.		None.	53% pravastin, 62% controls, *p*, NS.			No significant beneficial effect obtained with oral administration of pravastin. Pravastin may still be effective if administered far enough in advance of procedure for serum cholesterol to be lowered by time of PTCA.
Hoberg, *et al.*, 1994 Germany		None.			None.	Stable angina: 38% verapamil, 63% placebo, $p = 0.04$.			High-dose verapamil treatment reduced restenosis rate in patients with stable angina but not in unstable angina or non-Q-wave infarction patients. Only patients at increased risk for restenosis studied, so beneficial effect of verapamil possibly limited to this group.
Faxon, 1995 USA and Canada (MARCATOR study group)		0.3% placebo, 0.8% 1 mg, 0.6% 5 mg, 0.6% 10 mg.	14% placebo, 13% 1 mg, 13% 5 mg, 10% 10 mg.		2% placebo, 2% 1 mg, 2% 5 mg, 3% 10 mg.			Revascularisation: 15% placebo, 20% 1 mg, 17% 5 mg, 21% 10 mg.	Study demonstrates that cilazapril in doses ranging from low to high does not reduce restenosis.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Brack, *et al.*, 1995 UK (SHARP trial investigators)	Patients having successful PTCA for angiographically proven narrowing in ≥ 1 coronary artery. RCT, multicentre, blinded 299 patients (339 randomised)	Groups: 12,500 IU b.d. heparin (140), controls (159); taken for 4 months.	Male: 82% controls, 80% heparin. Mean age, years: 56 controls, 57 heparin. Single site dilated: 86% controls, 77% heparin. Stenosis pre-PTCA: 71% controls, 72% heparin. Stenosis post-PTCA: 32% controls, 35% heparin. Type A lesion: 34% controls, 35% heparin. Type B lesion: 52% controls, 57% heparin. Angina grade 3 or 4: 47% controls, 46% heparin. Diabetes: 7% controls, 5% heparin. Previous CABG: 4% controls, 2% heparin. Previous PTCA: 2% controls, 3% heparin.	4 months; 40 patients defaulted (13 (8%) controls, 27 (19%) heparin).
Savage, *et al.*, 1995 USA	Patients having successful PTCA of at least one lesion > 60% diameter stenosis. RCT, double-blind, multicentre 752 patients	Groups: aspirin, 325 mg/day (248), sulotroban, 880 mg/ 6 hours (249), placebo (255); taken for 6 months.	Male: 79% aspirin, 85% sulotroban, 81% placebo. Diameter stenosis: 79% aspirin, 80% sulotroban, 79% placebo. Length stenosis, mm: 11.6 aspirin, 11.4 sulotroban, 11.7 placebo. Mean age, years: 58 aspirin, 56 sulotroban, 58 placebo. Prior PTCA: 8% aspirin, 8% sulotroban, 9% placebo. Diabetes: 19% aspirin, 19% sulotroban, 17% placebo. Unstable angina: 44% aspirin, 56% sulotroban, 54% placebo.	6 months; 33% dropped from study (74 non-compliance, 57 adverse effects).
Tardiff, *et al.*, 1997 Canada	Probucol and multivitamins vs. placebo in prevention of restenosis. RCT, double-blind 317 patients	Probucol alone (n = 79) (Group 1) vs. multivitamins alone (beta-carotene + vitamin C + vitamin E) (78) (Group 2) vs. probucol + multivitamins (80) (Group 3) vs. placebo (80) (Group 4).	Mean age, years: Group 1, 60; 2, 58; 3, 58; 4, 59. % female: 1, 23; 2, 15; 3, 35; 4, 19. % smokers: 1, 15; 2, 24; 3, 15; 4, 21. Diabetes: 1, 9%; 2, 13%; 3, 155; 4, 5%. Angina grade II: 1, 62%;2, 67%; 3, 55%; 4, 54%. Grade III: 1, 23%; 2, 17%; 3, 23%; 4, 18%. 1-vessel disease: 1, 29%; 2, 49%; 3, 42%; 4, 35%. 2-vessel disease: 1, 49%; 2, 38%; 3, 35; 4, 43%. 3-vessel disease: 1, 22%; 2, 13%; 3, 23%; 4, 22%.	6 months.

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Brack, *et al.*, 1995 UK (SHARP trial investigators)		0.6% controls, 0.7% heparin.	33% controls, 32% heparin.			51% controls, 41% heparin, $p = 0.09$.	3% controls, 4% heparin.	8% controls, 4% heparin.	Heparin appears not to have therapeutic efficacy to reduce restenosis in humans. Perhaps before heparin is finally rejected, clinical trials should be conducted that match animal studies with continuous infusions or local targeted delivery.
Savage, *et al.*, 1995 USA		0.6% aspirin, 0% sulotroban, 0.6% placebo.			1.2% aspirin, 1.8% sulotroban, 5.7% placebo, $p < 0.05$ vs. placebo.	28% aspirin, 42% sulotroban, 35% placebo.			While aspirin and sulotroban reduce incidence of acute MI during follow-up, overall clinical outcome superior with aspirin. Thus, aspirin should be maintained in patients for minimum of 6 months after successful PTCA.
Tardiff, *et al.*, 1997 Canada						1, 21%; 2, 29%; 3, 43%; 4, 39%.		1, 11%; 2, 16%; 3, 24%; 4, 27%.	Probucol initiated 30 days before PTCA and given for 6 months prevents restenosis.

continued

Clinical effectiveness *contd*

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Topol, *et al.*, 1997 USA	Placebo-controlled trial of abciximab in patients at high risk. RCT, multicentre 2099 patients	Group 1, placebo bolus + infusion (662); group 2, abciximab 0.25/kg bolus (663); group 3, abciximab 0.25/kg bolus + 12-hour infusion at 10 µg/min (678).	Median age, years: Group 1, 61; 2, 60; 3, 62. Male: 1, 73.1%; 2, 72%; 3, 71.7%. Diabetes: 1, 25%; 2, 24%;3, 23%. Hypertension: 1, 55%; 2, 56%; 3, 54%. 1-vessel disease:1, 54%; 2, 52%;3, 56%. 2-vessel disease: 1, 29%; 2, 33%; 3, 31%. 3-vessel disease: 1, 17%; 2, 15%; 3, 13%. Previous bypass: 1, 15%; 2, 14%; 3, 16%. Previous PTCA: 1, 25%; 2, 20%; 3, 22%.	2.5–3 years.
Maresta, *et al.*, 1994 Italy (STARC study)	Patients aged 19–74 years, having successful PTCA for coronary stenosis ≥ 70% and documented significant ischaemia. RCT, double-blind, multicentre 254 patients	Groups: 300 mg trapidil 8-hourly (128), 100 mg ASA t.d.s. (126).	Males: 78% trapidil, 80% ASA. Mean age, years: 58.3 trapidil, 56.5 ASA. Diabetes: 17% trapidil, 7% ASA. Angina: 87% trapidil, 91% ASA. Stable angina: 69% trapidil, 82% ASA. Class III angina: 54% trapidil, 49% ASA. Class IV angina: 11% trapidil, 12% ASA.	6 months; 75 excluded from study as did not meet entry criteria (21 stopped treatment because of adverse events; 7 protocol violations; 23 refused angiogram and excluded from per protocol analysis).

Study	In-hospital mortality	Long-term mortality	Angina at follow-up	In-hospital MI rate	Long-term MI rate	Restenosis	CABG	Re-PTCA	Conclusions
Topol, *et al.*, 1997 USA		1-year: 5, 4, 4, respectively. 2-year: 7, 6, 5, respectively. 3-year: 9, 8, 7, respectively.			At 1 year: 11, 9, 8, respectively. At 2 years: 12, 11, 9, respectively. At 3 years: 14, 12, 11, respectively.			Revascularisation at – 1 year: 33, 30, 26, respectively. 2 years: 36, 35, 30, respectively. 3 years: 40, 39, 35, respectively.	Sustained benefit of treatment with abciximab in group at high risk.
Maresta, *et al.*, 1994 Italy (STARC study)		None.	No angina: 74% trapidil, 56% ASA. Class III: 8.6% trapidil, 13% ASA. Class IV: 3.9% trapidil, 8.7% ASA.		2.4% trapidil, 1.6% ASA.		0.8% trapidil, 0.8% ASA.		Trapidil shown to be effective in significantly reducing restenosis rates after coronary angioplasty in a randomised population. In addition, mean results for % stenosis at follow-up, final gain and loss of initial gain confirm its activity in preventing vessel reocclusion.

Cost and cost-effectiveness (primary data)

Study	Study characteristics	Treatment groups	Baseline characteristics	Follow-up
Mark, *et al.*, 1996 USA	Prospective multicentre cost analysis of the impact of abciximab on PTCA (attached to EPIC RCT).	See page 153. Abciximab bolus + infusion (AA) (n = 708); abciximab bolus only (AP) (n = 695); placebo (PP) (n = 696).	See page 153.	Perspective: partial health service (hospital); all patients included (97% retrieval of data). Data from 93% of 6-month survivors (n = 1923). Based on hospital costs derived form cost-to-charge ratios; includes medical costs and physician fees; excludes outpatient costs except for cardiac catheterisation. Expressed in US$; sources of costs not reported.

Study	Follow-up (duration of costing)	Results	Conclusions
Mark, *et al.*, 1996 USA	6 months.	Mean initial hospitalisation (SD), days: AA, 6.4 (7.0); AP, 6.1 (4.6); PP, 5.9 (5.8); *p*, NS. Mean initial hospital costs (sd), $: AA, 11,652 (9339); AP, 11,141 (6498); PP, 11,430 (11,170); *p*, NS. Mean cumulative 6-month medical costs (SD), $: AA, 16,792 (13,764); AP, 17,392 (11,141); PP, 17,999 (16,675); *p*, NS.	No significant impact on costs by use of abciximab after first 6 months. (NB: Data merged for 56 centres; final costs include those of 105 patients with incomplete costing data for whom costs were derived using multiple logistic regression analysis.)

Appendix 13

Quality assessment of included studies

Clinical effectiveness and health-related quality of life

This appendix includes a quality assessment of trials and observational studies included in the review of clinical effectiveness studies.

In addition, there is a quality assessment of the design and general methods of studies included in the health-related quality-of-life review (these studies are shown with an * by the authors' names). The quality assessment of RCTs of PTCA versus CABG was undertaken as part of the meta-analysis described in the main text.

RCTs of medical therapies (see appendix 4)

Study	Randomisation	Follow-up (> 80%)	Withdrawals assessed and included	Blinded assessment of outcomes	Comparable groups	Groups treated identically?
Destors, *et al.,* 1989	Described	Yes	Yes	Yes	Yes	Yes
Loaldi, *et al.,* 1991	Stated	Yes	Yes	Yes	Yes	Yes
Vliegen, *et al.,* 1991	Stated	Yes	No	Yes	Yes	Yes
Boberg, *et al.,* 1992	Stated	Yes	Yes	Yes	Yes	Yes
Kawanishi, *et al.,* 1992	Stated	Yes	Yes	Yes	Yes	Yes
Nahrendorf, *et al.,* 1992	Stated	Yes	Assessed, not included	Yes	Yes	Yes
Guermonprez, *et al.,* 1993	Described	Yes	Yes	Yes	Yes	Yes
Rehnqvist, *et al.,* 1996	Stated	Yes	Yes	Unclear	Yes	Yes
Singh, 1993	Stated	Yes	Yes	Yes	Yes	Yes
Dargie, *et al.,* 1996	Stated	Yes	Yes	Yes	Yes	Yes

Observational studies of medical therapies (see appendix 4)

Study	Representative	Inclusion criteria	Similar entry point	Follow-up	Objective assessment of outcomes	Comparisons: sufficient information?
McKenna, *et al.,* 1994*	Yes	Yes	Yes	Yes	Yes	Yes
Spertus, *et al.,* 1994; 1995*	No	No	Yes	Yes	Yes	N/A

* *Study included in HRQoL review*

RCTs of medical therapies versus CABG (see appendix 5)

Study	Randomisation	Follow-up (> 80%)	Withdrawals assessed and included	Blinded assessment of outcomes	Comparable groups	Groups treated identically?
Manske, *et al.,* 1992	Stated	Yes	Yes	Yes	Yes	Yes
Bhayana, *et al.,* 1980	Described	No	Yes (intention-to-treat)	No	Yes	Yes
VA Coronary Artery Bypass Surgery Cooperative Study Group, 1992	Stated	Yes	Yes	Yes	Yes	Yes
Takaro, *et al.,* 1985	Stated	Yes	No	No	Yes	No
Alderman, *et al.,* 1990	Stated	Yes	Yes	No	No	No
Palac, *et al.,* 1981	Stated	No	No	Yes	Yes	Yes
Frick, *et al.,* 1983	Described	Yes	Yes	No	Yes	Yes
Gersh, *et al.,* 1985	Stated	Yes	Yes	No	No	Yes
Hwang, *et al.,* 1990	Stated	Unclear	No	No	Not specified	Not specified
Rogers, *et al.,* 1990*	Stated	Yes	Yes	No	?	No

* *Study included in HRQoL review*

RCTs of medical therapy versus PTCA (see appendix 6)

Study	Randomisation	Follow-up (> 80%)	Withdrawals assessed and included	Blinded assessment of outcomes	Comparable groups	Groups treated identically?
Pepine, *et al.,* 1994; Davies, *et al.,* 1997	Stated	Yes	N/A	No	Yes	Yes
Folland, *et al.,* 1997	Stated	Yes	Yes	Yes	Yes	Unclear
Hueb, *et al.,* 1995	Stated	Yes	Yes	No	Yes	Yes
RITA-2 trial participants, 1997	Described	Yes	Yes	Yes	Yes	Yes
Strauss, *et al.,* 1995*	Described	Yes	Yes	Yes	Yes	Yes

* *Study included in HRQoL review*

Studies comparing CABG and PTCA in HRQoL (see appendix 7)

Study	Representative	Inclusion criteria	Similar entry point	Follow-up	Objective assessment of outcomes	Comparisons: sufficient information?
Pocock, *et al.,* 1996*	Yes	Yes	Yes	Yes	Yes	Yes
Papadantonaki, *et al.,* 1994*	Yes	Yes	Yes	No	Yes	Yes
Hlatky, *et al.,* 1995; 1997*	Yes	Yes	Yes	Yes	Yes	Yes

* *Study included in HRQoL review*

Observational studies of CABG (see appendix 8)

Study	Representative	Inclusion criteria	Similar entry point	Follow-up	Objective assessment of outcomes	Comparisons: sufficient information?
Acinapura, *et al.,* 1989	Yes	Yes	No	Yes	Yes	Yes
Acinapura, *et al.,* 1992	Yes	Yes	No	Yes	Yes	Yes
Azariades, *et al.,* 1990	No	Yes	No	Yes	Yes	Yes
Bell, *et al.,* 1992	Yes	Yes	Yes	Yes	Yes	Yes
Barner, *et al.,* 1985	Yes	Yes	No	Yes	Yes	No
Brandrup-Wognsen, *et al.,* 1995	Yes	No	Yes	Yes	Yes	N/A
Cameron, *et al.,* 1995	Yes	Yes	Not specified	Yes	Yes	Yes
Canver, *et al.,* 1996	Yes	No	Yes	Yes	Yes	No
Christakis, *et al.,* 1992	Yes	Yes	Yes	Yes	No	Yes
Christakis, *et al.,* 1993	Yes	Yes	Yes	No	Yes	Yes
Fitzgibbon, *et al.,* 1996	Unclear	Yes	No	Yes	Yes	No
Gersh, *et al.,* 1983	Yes	Yes	Yes	No	Yes	Yes
Jaglal, *et al.,* 1995	Yes	Yes	Yes	No	Yes	Yes
Jones & Wientraub, 1996	Yes	Yes	Unclear	Yes	No	Yes
Killen, *et al.,* 1982b	Yes	Yes	No	Yes	Yes	Yes
Laird-Meeter, *et al.,* 1984	Yes	Yes	Yes	Yes	Yes	Yes
Laird-Meeter, *et al.,* 1987a, b	Yes	Yes	Yes	Yes	Yes	Yes
Liao, *et al.,* 1992	Yes	Yes	Yes	Yes	Yes	Yes
Maddern, *et al.,* 1984	Yes	No	No	Yes	Yes	Yes
Mantia, *et al.,* 1994	N/A	No	No	Yes	Yes	Yes
MacManus, *et al.,* 1990	Yes	Yes	No	Yes	Yes	Yes
Mickleborough, *et al.,* 1995	Yes	Yes	Yes	Yes	Yes	Yes
Peterson, *et al.,* 1995	No	Yes	No	Yes	Yes	Yes
King, *et al.,* 1992a	Yes	Yes	No	No	Yes	Yes
Morris, *et al.,* 1990	Yes	Yes	No	Yes	Yes	Yes
Rahimtoola, *et al.,* 1993a, b	Yes	Yes	Yes	Yes	Yes	Yes
Risum, *et al.,* 1995	Yes	Yes	Yes	Yes	Yes	Yes
Risum, *et al.,* 1996	Yes	Yes	Yes	Yes	No	Yes
Richardson & Cyrus, 1986	Yes	Yes	Yes	Yes	Yes	Yes
Salomon, *et al.,* 1990	Yes	Yes	Yes	Yes	Yes	Yes
Sheldon & Loop, 1984	Yes	Yes	Yes	Yes	Yes	Yes

continued

Observational studies of CABG *contd* (see appendix 8)

Study	Representative	Inclusion criteria	Similar entry point	Follow-up	Objective assessment of outcomes	Comparisons: sufficient information?
Schmuziger, *et al.,* 1994	Yes	Yes	Yes	Yes	Yes	Yes
Stahle, *et al.,* 1991	Yes	Yes	Yes	Yes	Yes	Yes
Teoh, *et al.,* 1987	Yes	Yes	Yes	Yes	Yes	Yes
Tyras, *et al.,* 1980	Yes	Yes	No	Yes	Yes	Yes
Weintraub, *et al.,* 1995a	Yes	Yes	Yes	Yes	Yes	Yes
Muhlbaier, *et al.,* 1992 (also medical treatment)	Yes	Yes	No	Yes	Yes	Yes

Observational studies: HRQoL outcomes of CABG (see appendix 8)

Study	Representative	Inclusion criteria	Similar entry point	Follow-up	Objective assessment of outcomes	Comparisons: sufficient information?
Permanyer-Miralda, *et al.,* 1991*	Unclear	Yes	No	Yes	Yes	Yes
Mayou & Bryant, 1987*	Yes	No	Unclear	Yes	Yes	Yes
Caine, *et al.,* 1991*	Yes	Yes	Yes	Yes	Yes	Yes
Kallis, *et al.,* 1993*	Yes	Yes	Unclear	Yes	Yes	Yes
Sjoland, *et al.,* 1996*	Unclear	No	Yes	Yes	Yes	Yes
Steine, *et al.,* 1996*	Yes	Yes	Yes	Yes	Yes	Yes
King, *et al.,* 1992b*	Yes	No	Yes	Yes	Yes	Yes

* *Study included in HRQoL review*

RCTs of medical adjuncts to CABG (see appendix 9)

Study	Randomisation	Follow-up (> 80%)	Withdrawals assessed and included	Blinded assessment of outcomes	Comparable groups	Groups treated identically?
Azen, *et al.,* 1996	Stated	Yes	Yes	Yes	Yes	Yes
Brown, *et al.,* 1985	Stated	Yes	Yes	Yes	Unclear	Yes
Mayer, *et al.,* 1981	Described	No	No	Yes	No	Yes
Gerschlick, *et al.,* 1988	Stated	Yes	No	Yes	Unclear	Yes
Rajah, *et al.,* 1985	Stated	Yes	Yes	Yes	Yes	Yes
McEnany, *et al.,* 1982	Described	Yes	Yes	No	Yes	Yes
Myhre, *et al.,* 1984	Stated	Yes	Yes	No	Unclear	No
Oka, *et al.,* 1980	Stated	Yes	Yes	No	Yes	Yes
van der Meer, *et al.,* 1993	Described	Yes	Yes (intention-to-treat)	Yes	Yes	Yes

Observational studies of HRQoL or other outcomes following PTCA (see appendix 10)

Study	Representative	Inclusion criteria	Similar entry point	Follow-up	Objective assessment of outcomes	Comparisons: sufficient information?
Englehart, 1993*	Unclear	Yes	Unclear	Yes	Yes	Yes
Gulanick & Naito, 1994*	Yes	Yes	No	Yes	Yes	Yes
Malenka, 1996*	No	Yes	No	Yes	Yes	Yes
* *Study included in HRQoL review*						

RCTs of non-medical adjuncts to PTCA (see appendix 11)

Study	Randomisation	Follow-up (> 80%)	Withdrawals assessed and included	Blinded assessment of outcomes	Comparable groups	Groups treated identically?
Topol, *et al.,* 1993b	Described	Yes	Yes (intention-to-treat)	Yes	Yes	Yes
Adelman, *et al.,* 1993	Described	Yes	Yes (intention-to-treat)	Yes	No	Yes
Fischman, *et al.,* 1994	Described	Yes	No	No	Yes	No
Holmes, *et al.,* 1995	Described	Yes	Yes	Yes	No	Yes
Macaya, *et al.,* 1996	Described	Yes	Yes (intention-to-treat)	Yes	Yes	No
Sirnes, *et al.,* 1996	Described	Yes	Yes	No	Yes	No
Versaci, *et al.,* 1997	Stated	Yes	Yes	No	Yes	Yes
Reifart, *et al.,* 1997	Described	Yes	Yes	No	Yes	Yes
Teirstein, *et al.,* 1997	Stated	Yes	Yes	Yes	Yes	Yes
Appelman, *et al.,* 1996	Described	Yes	Yes (intention-to-treat)	Yes	Yes	Yes
Cohen, *et al.,* 1997	Described	Yes	Yes	Yes	Yes	Yes

Observational studies of non-medical adjuncts to PTCA (see appendix 11)

Observational study	Representative	Inclusion criteria	Similar entry point	Follow-up	Objective assessment of outcomes	Comparisons: sufficient information?
Altmann, *et al.,* 1996	Yes	Yes	No	Yes	Yes	Yes
Karrillon, *et al.,* 1996	Yes	Yes	No	1 month	No	Yes

RCTs of medical adjuncts to PTCA (see appendix 12)

Study	Randomisation	Follow-up (> 80%)	Withdrawals assessed and included	Blinded assessment of outcomes	Comparable groups	Groups treated identically?
Brack, *et al.,* 1995	Stated	Yes	Yes	Yes	Yes	Yes
Corcos, *et al.,* 1985	Described	Yes	N/A (Yes)	No	Yes	Yes
Darius, *et al.,* 1992	Stated	Yes	N/A (Yes)	Yes	No data	Yes
EPIC investigators, 1994	Described	Yes	Yes (intention-to-treat)	Yes	Yes	Yes
Faxon, *et al.,* 1994	Stated	Yes	Yes (intention-to-treat)	Yes	Yes	Yes
Faxon, 1995	Stated	No	Yes (intention-to-treat)	Yes	Yes	Yes
Gerschlick, *et al.,* 1994	Stated	Yes	Yes	Yes	Yes	Yes
Hoberg, *et al.,* 1994	Stated	Yes	Yes	Yes	No	Yes
Maresta, *et al.,* 1994	Stated	Yes	Yes (intention-to-treat)	Yes	Unclear	Yes
Nye, *et al.,* 1990	Stated	Yes	No	No	Not specified	Yes
MERCATOR study group, 1992	Stated	Yes	Yes (intention-to-treat)	Yes	Yes	Yes
O'Keefe, *et al.,* 1991	Stated	No	No	No	Yes	Yes
Onaka, *et al.,* 1994	Pseudo	Yes	Yes	No	Yes	Yes
Savage, *et al.,* 1995	Described	Yes	Yes	Yes	Yes	Yes
Stone, *et al.,* 1989	Described	No	No	No	Yes	Yes
Tardiff, *et al.,* 1997	Stated	Yes	Yes	Yes	Yes	Yes
Topol, *et al.,* 1997	Stated	Yes	Yes	Yes	Yes	Yes
Thornton, *et al.,* 1984	Stated	Yes	No	No	Yes	Yes

RCTs of medical adjuncts to stenting (see appendix 12)

Study	Randomisation	Follow-up (> 80%)	Withdrawals assessed and included	Blinded assessment of outcomes	Comparable groups	Groups treated identically?
Hall, *et al.,* 1996	Stated	Yes	No	Yes	No (some significant differences)	Yes
Schomig, 1996	Yes	Yes	Yes (intention-to-treat)	No	Yes	Yes

Health-related quality of life

Study	Detailed in appendix	Instrument(s)	Reviewed in Bowling, 1991 or 1995?
Fletcher, *et al.,* 1988	4	(a) SIP (b) Health Index	(a) Yes (b) No
Blake, *et al.,* 1992	4	Patients' preferences	
Rogers, *et al.,* 1990	5	No formal instruments[a]	
Strauss, *et al.,* 1995	6	MHIQ	Yes
Spertus, *et al.,* 1994; 1995	6	SAQ	No
Papadantonaki, *et al.,* 1994	7	(a) QLI Cardiac III (b) POMS	(a) Yes (b) Yes
Pocock, *et al.,* 1996	7	NHP	Yes
Cameron, *et al.,* 1994	7	York QALY Toolkit using Rosser Matrix	Yes
Hltatky, *et al.,* 1995	7	(a) Duke Activity Status Index (b) Mental Health Inventory (c) RAND	(a) No (b) No (c) Yes
Mayou & Bryan, 1987	8	(a) Present State Examination (b) POMS (c) WAIS-R	(a) Yes (b) Yes (c) No
Langeluddecke, *et al.,* 1989	8	(a) PAIS (b) Pleasant Events Schedule (c) CESD (d) Spielberger State Anxiety Inventory	(a) Yes (b) No (c) Yes (d) Yes
Caine, *et al.,* 1991	8	NHP	Yes
Permanyer-Miralda, *et al.,* 1991	8	NHP	Yes
King, *et al.,* 1992b	8	(a) Satisfaction with Life Scale (b) POMS (c) SIP	(a) Yes (b) Yes (c) Yes
Kallis, *et al.,* 1993	8	Rosser Matrix	Yes
Gold, *et al.,* 1995	8	(a) CESD (b) SF-36	(a) Yes (b) Yes
Sjoland, *et al.,* 1996	8	(a) PGWB (b) NHP (c) Angina Pectoris Quality of Life Questionnaire	(a) Yes (b) Yes (c) No
Steine, *et al.,* 1996	8	(a) 30-item General Health Questionnaire (b) Family APGAR score	(a) Yes (b) No
Klonoff, *et al.,* 1989	8	WAIS-R	No
Flynn & Frantz, 1987	8	No formal instruments[b]	
McKenna, *et al.,* 1994	10	(a) Total Life Satisfaction score (b) PGWB	(a) Yes (b) Yes

[a] Given the dearth of information on HRQoL in this area, this study was included despite the absence of a formal instrument.

[b] Although no formal instrument used, authors refer to validation work undertaken on their questionnaire, so this study included.

Cost and cost-effectiveness analysis

Each economic analysis included in the review was assessed, by one reviewer, against the referees' checklist developed for economic articles submitted to the *BMJ* (Drummond & Jefferson, 1996). Briefly, the checklist consists of 35 items divided into three parts: study design, data collection, and analysis and interpretation of results. The results of the exercise are detailed below.

Study design

Article	Checklist items*						
	1	2	3	4	5	6	7
Cohen, *et al.,* 1995	Yes	Yes	Yes	Yes	Yes	Yes	No
Cohen, *et al.,* 1994	Yes	Yes	Yes	Yes	Yes	Yes	No
Weinstein & Stason, 1982	Yes	Yes	Yes	Yes	Yes	Yes	No
Wong, *et al.,* 1990	Yes	Yes	N/C	Yes	Yes	N/C	No
Sculpher, *et al.,* 1994	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rodriguez, *et al.,* 1993	Yes	N/C	N/C	Yes	Yes	N/C	N/C
Cohen, *et al.,* 1993	Yes	Yes	Yes	N/C	N/C	Yes	Yes
Cohen & Baim, 1995	Yes	Yes	Yes	Yes	Yes	N/C	N/C
Guzman, *et al.,* 1994	Yes	Yes	Yes	Yes	Yes	N/C	N/C
Topol, *et al.,* 1993a	N/C	N/C	N/C	Yes	Yes	No	N/C
Dick, *et al.,* 1991	Yes	Yes	Yes	Yes	Yes	Yes	Yes
van den Brand, *et al.,* 1990	Yes	Yes	No	Yes	Yes	N/C	N/C
Wientraub, *et al.,* 1995c	Yes	Yes	N/C	Yes	Yes	N/C	N/C
Hlatky, *et al.,* 1990	Yes	Yes	No	Yes	Yes	No	No
Black, *et al.,* 1988	Yes	Yes	No	No	Yes	No	No
Kelly, *et al.,* 1985	Yes	Yes	No	Yes	Yes	No	No
Dougenis, *et al.,* 1992	Yes	Yes	N/C	Yes	Yes	Yes	No
Mark, *et al.,* 1996	Yes	Yes	N/C	Yes	Yes	N/C	N/C
Charles, *et al.,* 1982	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jang, *et al.,* 1984	Yes	Yes	Yes	Yes	Yes	Yes	N/C
Goods, *et al.,* 1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kinlay, 1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Larratt, 1994	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wittels, *et al.,* 1990	Yes	Yes	Yes	Yes	Yes	N/C	N/C
Williams, 1985	Yes	Yes	Yes	Yes	Yes	Yes	No

* *1: Research question stated.*
2: Economic importance of research question stated.
3: Viewpoint(s) of analysis clearly stated and justified.
4: Rationale for choosing alternative programmes or interventions compared stated.
5: Alternatives being compared clearly described.
6: Form of economic evaluation used stated.
7: Choice of form of economic evaluation justified in relation to questions addressed.

N/C, not clear

Data collection

Article	Checklist items*													
	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Cohen, *et al.,* 1995	Yes	N/A	Yes	Yes	Yes	N/C	N/A	N/A	No	Yes	Yes	Yes	Yes	Yes
Cohen, *et al.,* 1994	Yes	N/A	Yes	Yes	Yes	N/C	N/A	N/A	No	Yes	Yes	Yes	Yes	Yes
Weinstein & Stason, 1982	Yes	N/A	No	Yes	Yes	N/A	N/A	N/A	No	Yes	Yes	Yes	N/C	N/C
Wong, *et al.,* 1990	Yes	N/A	Yes	Yes	No	No	N/A	N/A	No	No	Yes	Yes	Yes	N/C
Sculpher, *et al.,* 1994	Yes	Yes	N/A	Yes	N/A	N/A	N/A	N/A	Yes	Yes	Yes	Yes	N/A	N/A
Rodriguez, *et al.,* 1993	Yes	Yes	N/A	N/C	N/A	N/A	N/A	N/A	No	No	Yes	No	No	No
Cohen, *et al.,* 1993	Yes	Yes	N/A	Yes	N/A	N/A	N/A	N/A	Yes	Yes	Yes	No	N/A	N/A
Cohen & Baim, 1995	Yes	Yes	N/A	N/C	No	No	No	No	No	Yes	Yes	No	No	No
Guzman, *et al.,* 1994	Yes	Yes	N/A	N/C	N/A	N/A	No	No	No	Yes	Yes	No	No	No
Topol, *et al.,* 1993a	Yes	Yes	N/A	N/C	N/C	No	No	No	No	No	No	N/C	No	No
Dick, *et al.,* 1991	No	N/A	N/A	N/C	N/A	N/A	No	No	No	Yes	N/C	No	N/A	N/A
van den Brand, *et al.,* 1990	No	?	N/A	No	N/A	N/A	N/A	N/A	N/C	Yes	Yes	Yes	N/A	N/A
Wientraub, *et al.,* 1995c	Yes	Yes	N/A	N/C	N/C	Yes	No	No	Yes	Yes	Yes	Yes	No	No
Hlatky, *et al.,* 1990	N/C	?	N/C	No	No	No	No	No	Yes	Yes	Yes	No	No	No
Black, *et al.,* 1988	Yes	Yes	N/A	Yes	N/C	Yes	N/A	N/A	Yes	No	N/C	No	No	No
Kelly, *et al.,* 1985	Yes	Yes	N/A	Yes	N/C	Yes	N/A	N/A	Yes	No	N/C	No	No	No
Dougenis, *et al.,* 1992	Yes	Yes	N/A	Yes	Yes	Yes	No	No	N/C	Yes	Yes	Yes	N/A	N/A
Mark, *et al.,* 1996	Yes	Yes	N/A	N/C	No	No	No	No	Yes	Yes	N/C	No	No	No
Charles, *et al.,* 1982	Yes	Yes	N/A	Yes	N/A	N/A	N/A	N/A			Yes	No	N/A	N/A
Jang, *et al.,* 1984	Yes	Yes	N/A	Yes	N/A	N/A	N/A	N/A	No	N/C	N/C	N/C	N/A	N/A
Goods, *et al.,* 1996	Yes	Yes	N/A	Yes	N/A	N/A	N/A	N/A	Yes	N/C	N/C	No	N/A	N/A
Kinlay, 1996	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	No	Yes	Yes	No	Yes	Yes
Larratt, 1994	Yes	N/A	N/C	Yes	No	No	N/A	N/A	N/C	Yes	Yes		Yes	Yes
Wittels, *et al.,* 1990	N/C	N/A	Yes	Yes	N/C	No	N/A	N/A	No	Yes	Yes	No	Yes	Yes
Williams, 1985	Yes	No	No	Yes	Yes	N/C	N/A	N/A	No	No	Yes	No	Yes	Yes

* *8: Source(s) of effectiveness estimates are stated.*
9: Details of design and results of effectiveness study given (if based on single study).
10: Details of method of synthesis or meta-analysis of estimates given (if based on overview of number of effectiveness studies).
11: Primary outcome measure(s) for economic evaluation clearly stated.
12: Methods to value health states and other benefits stated.
13: Details of subjects from whom valuations were obtained given.
14: Productivity changes (if included) reported separately.
15: Relevance of productivity changes to study question discussed.
16: Quantities of resources reported separately from their unit costs.
17: Methods for estimation of quantities and unit costs described.
18: Currency and price data recorded.
19: Details of currency and price adjustments for inflation or currency conversion given.
20: Details of any model used given.
21: Choice of model used and key parameters on which it is based justified.

N/C, not clear; N/A, not applicable

Analysis and interpretation of results

Article	Checklist items*													
	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Cohen, *et al.,* 1995	Yes	Yes	No	N/A	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cohen, *et al.,* 1994	Yes	Yes	No	N/A	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Weinstein & Stason, 1982	Yes	Yes	No	N/A	N/A	Yes	Yes	N/C	Yes	Yes	Yes	Yes	Yes	Yes
Wong, *et al.,* 1990	N/C	Yes	No	N/A	N/A	Yes	Yes	N/C	Yes	Yes	Yes	Yes	Yes	Yes
Sculpher, *et al.,* 1994	Yes	Yes	Yes	N/A	Yes	N/A	N/A	N/A	Yes	N/A	Yes	Yes	Yes	Yes
Rodriguez, *et al.,* 1993	Yes	N/A	N/A	N/A	No	No	No	No	Yes	No	Yes	N/C	Yes	No
Cohen, *et al.,* 1993	Yes	N/A	N/A	N/A	Yes	N/C	N/C	N/C	Yes	Yes	N/C	Yes	Yes	Yes
Cohen & Baim, 1995	Yes	No	No	No	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes
Guzman, *et al.,* 1994	Yes	No	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Topol, *et al.,* 1993a	Yes	No	No	No	N/C	No	No	No	Yes	N/C	No	N/C	N/C	No
Dick, *et al.,* 1991	Yes	No	No	No	Yes	No	No	No	N/C	Yes	No	Yes	Yes	Yes
van den Brand, *et al.,* 1990	Yes	No	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes
Wientraub, *et al.,* 1995c	Yes	No	No	No	Yes	No	No	No	Yes	Yes	N/C	Yes	Yes	N/C
Hlatky, *et al.,* 1990	No	No	No	No	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes
Black, *et al.,* 1988	Yes	No	No	No	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes
Kelly, *et al.,* 1985	Yes	No	No	No	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes
Dougenis, *et al.,* 1992	Yes	No	No	No	Yes	No	No	No	No	Yes	Yes	No	Yes	N/C
Mark, *et al.,* 1996	Yes	No	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Charles, *et al.,* 1982	Yes	N/A	N/A	N/A	Yes	N/A	N/A	N/A		No	Yes	Yes	Yes	Yes
Jang, *et al.,* 1984	Yes	N/A	N/A	N/A	Yes	Yes	Yes	Yes	Yes	Yes	N/C	Yes	Yes	N/C
Goods, *et al.,* 1996	Yes	N/A	N/A	N/A	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kinlay, 1996	Yes	Yes	No	N/A	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Larratt, 1994	Yes	N/A	N/A	No	N/A	No	No	No		Yes	N/C	Yes	Yes	Yes
Wittels, *et al.,* 1990	Yes	No	No	No	N/A	No	No	No	Yes	No	N/C	N/C	N/C	Yes
Williams, 1985	No	Yes	No	N/A	N/A	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes

* *22: Time horizon of costs and benefits stated.*
23: Discount rate(s) stated.
24: Choice of rate(s) justified.
25: Explanation given if costs or benefits not discounted.
26: Details of statistical tests and CIs given for stochastic data.
27: Approach to sensitivity analysis given.
28: Choice of variables for sensitivity analysis justified.
29: Ranges over which variables are varied stated.
30: Relevant alternatives compared.
31: Incremental analysis reported.
32: Major outcomes presented in dis-aggregated as well as aggregated form.
33: Answer to study question given.
34: Conclusions follow from data reported.
35: Conclusions accompanied by appropriate caveats.

N/C, not clear; N/A, not applicable

Further comments

Article	Comments relating to quality
Cohen, *et al.,* 1995	Costs reported, outcomes reported, not actually linked. Basically a cost-effectiveness analysis; economic parameter is average 1-year cost per patient.
Guzman, *et al.,* 1994	Cost reported, outcomes reported, not actually linked.
Topol, *et al.,* 1993a	Quality-of-life measures reported as measured but no results reported. Control and patients used for costs not reported. Year and sources of charges not reported. Reports restenosis rates for alternatives but does not link outcomes with costs.
Dick, *et al.,* 1991	Sources of charges not reported.
van den Brand, *et al.,* 1990	
Hlatky, *et al.,* 1990	Year of costs not reported. Excluded costs not explicitly reported.
Black, *et al.,* 1988	In-hospital costs only. Year not reported. Charges not costs.
Kelly, *et al.,* 1985	Mortality and re-interventions recorded only. Year and source of costs not reported. Charges not costs. No sensitivity analysis.
Dougenis, *et al.,* 1992	Costs reported for individual items but not resource use.
Mark, *et al.,* 1996	Some sources not reported.
Charles, *et al.,* 1982	Cost analysis. Outcomes reported but not linked to costs.

Appendix 14

An example of decision analysis in stable angina: a framework for reviewing management patterns (prepared by Robin Dowie)

Late in 1995, Somerset Health Authority reviewed its contracts for cardiac revascularisation procedures and the volumes of CABGs and PTCAs that it was purchasing. The health authority is unusual in having access to routinely recorded morbidity data generated by 12 local general practices (the Somerset Morbidity Project). Thus, it was possible for the authority reliably to predict, for the county of Somerset, the incidence of newly diagnosed cases of stable angina in general practice.

Somerset Health Authority was already associated with a Department of Health project on developing guidance for purchasers of cardiac services for which decision analysis was being used as a framework technique. (South Lancashire Health Authority was also involved in the project but its work focused primarily on pre-hospital acute care, Dowie, *et al.*, 1998.) At Somerset's request, a decision-analytic framework was developed for predicting volumes of revascularisation procedures for cohorts of newly diagnosed angina patients based on current practice (Dowie, 1996b).

An outline of the framework is shown in *Figure 2*. It begins with the diagnosis of 'typical' angina reached by a GP for a patient with a first presentation or a re-presentation of anginal symptoms. (The doctor might choose to begin by treating the patient with anti-anginal agents; the fully articulated version of the framework distinguishes

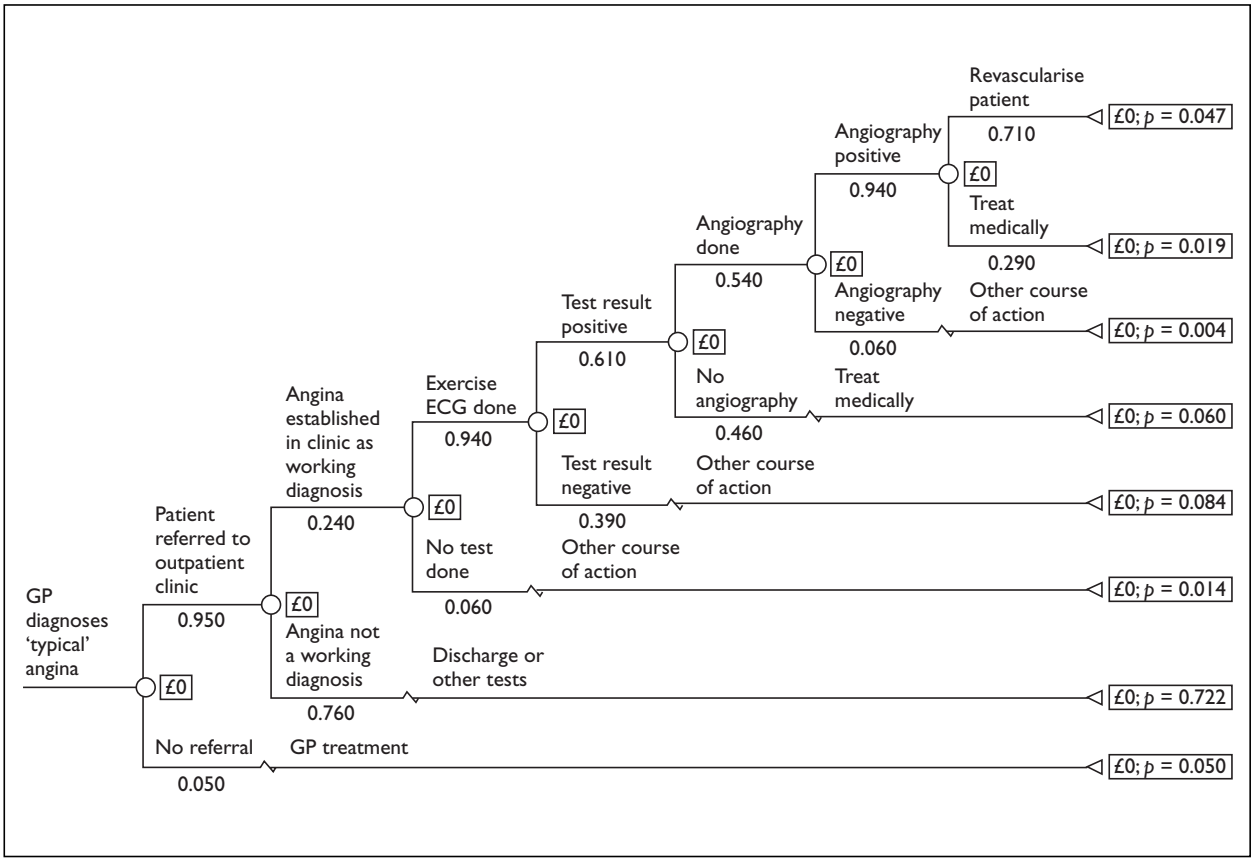

FIGURE 2 *An outline of the framework. No costs have been included in the analysis, hence the £0 annotations.*

between treatment or no treatment with beta-blocker pharmaceuticals, and between a history or no history of MI.) Modelled on the outline tree are the chief cardiac investigations undertaken for patients with stable angina. The branches terminate with outcome states, such as revascularisation, medical treatment, or another course of action.

Probability values for entering in the fully articulated angina framework were derived from a range of source documents, almost all of which were reports of observational studies. Particular problems were experienced in finding results in papers which met the pre-conditions in the framework. For instance, published data on patients undergoing coronary angiography do not normally distinguish between patients newly diagnosed with stable angina and patients suffering from chronic stable angina. Nonetheless, baseline probability values were assessed to allow the framework to be analysed. Costs were not entered at this stage. The analysis indicated that, at the present time, patients newly diagnosed in general practice as having stable angina and who are referred to a hospital medical outpatient clinic have a 5% chance of being identified for revascularisation within the next few months.

The final stage of the analysis was to estimate the likely caseload of revascularised patients for Somerset Health Authority, based on the annual incidence rate for new angina cases derived from the Somerset Morbidity database. Assumptions had to be made about the rates of referral of Somerset GPs; nationally available information on angina referral rates is not reliable. Nevertheless the evidence suggests that the rate may be in the order of 20% (across all age groups). When this rate was entered in the framework, the overall probability of a newly diagnosed patient in general practice being identified for revascularisation was reduced to less than 1%, and the total revascularisation caseload for a cohort of 2320 newly diagnosed patients was of the order of 20 patients.

The conclusion drawn from this exercise is that commissioners, when formulating contracts for coronary revascularisation, need access to information on patterns of treatment for patients with chronic stable angina as well as for patients suffering from acute MI and unstable angina.

To illustrate the method of decision analysis, the outline tree contains probability values derived from a study in Southampton in which local GPs agreed to refer to an newly established chest pain clinic all men and women presenting for the first time with chest pain which, in the GPs' opinion, could be stable angina. In all, 467 patients were referred (Gandhi, *et al.,* 1995a, and personal communication). The probability values entered in the outline include a GP referral rate of 95%. When the tree was analysed by 'folding back', the probability of a patient being identified for revascularisation was shown to be $p = 0.047$ (i.e. 5%). It seems unlikely, however, that GPs in their day-to-day practice are referring almost all their newly diagnosed cases of typical angina.

This modelling may be compared with a computer simulation model of pathways of coronary care developed by Bensley and colleagues (1995). The model is based on a flow chart, one half of which describes the pathways by which a patient can be selected for coronary angiography. The authors did not model explicitly the sequence of likely events occurring between referral to hospital and selection for coronary angiography. Rather, they relied on a pooling of clinicians' estimates. A baseline of 36% (representing the proportion of referred outpatient attenders aged 35–74 years who went forward for angiography) was entered in the model. The comparative rate in the Southampton study (modelled above) is 7% (for new clinic attenders under 71 years), while decision-analytic modelling of Bournemouth data on patients of any age referred to a direct access exercise test produced a rate of 17% for referred patients who were subsequently catheterised (Crook, *et al.,* 1994).

Decision analysis is valuable both for research and for informing commissioning practice. When applied to research, the technique can:

- frame the question under examination and identify all interrelated variables for which data (including possibly costings and outcome valuations) need to be collected to fully answer the research hypotheses
- identify variables for which it is not reasonable or practical to collect empirical data and for which other techniques will have to be used for assessing baseline probability values (e.g. the Delphi technique for obtaining expert judgements)
- rigorously examine, by the use of sensitivity analysis, conclusions derived from analysing ('folding back') the model
- ensure that, in published research reports, the results are presented comprehensively to allow readers to assess and use them in their own work.

From a commissioning perspective, decision analysis or simply the process of developing decision trees for 'framing' services can provide a means of:

- prioritising information requirements
- identifying and comparing options at each stage in the process of delivering care
- improving communications within and between separate interest groups of clinicians and managers, and providers and commissioners.

The decision-analytic approach can frame discussions whenever a conflict arises between the objectives of maximising clinical effectiveness for treating individuals and optimising cost-effectiveness for treating patient groups, although the approach will not, of course, resolve the conflict. Commissioners will, at the very least, be able to present a rationale for their decisions when faced with criticism.

Health Technology Assessment panel membership

This report was identified as a priority by the Acute Sector Panel.

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