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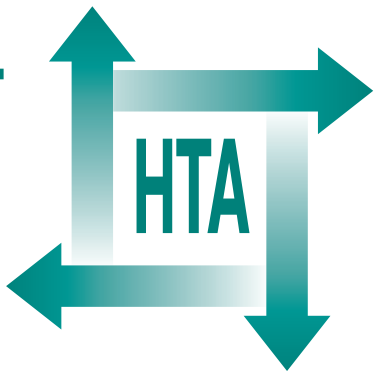

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A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery

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[1] Bristol Heart Institute, University of Bristol, Bristol Royal Infirmary, UK
[2] Department of Cardiac Surgery, Glenfield NHS Trust, Leicester, UK
[3] Department of Cardiology, Glenfield NHS Trust, Leicester, UK
[4] Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK
[5] Department of Cardiothoracic Surgery, Manchester Heart Centre, Manchester Royal Infirmary, UK
[6] Department of Cardiology, Manchester Heart Centre, Manchester Royal Infirmary, UK
[7] Department of Surgery, St Mary's NHS Trust, London, UK
[8] Department of Cardiology, St Mary's NHS Trust, London, UK

* Corresponding author. Contact address: Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK

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Abstract

A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery

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[1] Bristol Heart Institute, University of Bristol, Bristol Royal Infirmary, UK
[2] Department of Cardiac Surgery, Glenfield NHS Trust, Leicester, UK
[3] Department of Cardiology, Glenfield NHS Trust, Leicester, UK
[4] Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK
[5] Department of Cardiothoracic Surgery, Manchester Heart Centre, Manchester Royal Infirmary, UK
[6] Department of Cardiology, Manchester Heart Centre, Manchester Royal Infirmary, UK
[7] Department of Surgery, St Mary's NHS Trust, London, UK
[8] Department of Cardiology, St Mary's NHS Trust, London, UK
* Corresponding author. Contact address: Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK

Objectives: To compare the clinical- and cost-effectiveness of minimally invasive direct coronary artery bypass grafting (MIDCAB) and percutaneous transluminal coronary angioplasty (PTCA) with or without stenting in patients with single-vessel disease of the left anterior descending coronary artery (LAD).
Design: Multi-centre randomised trial without blinding. The computer-generated sequence of randomised assignments was stratified by centre, allocated participants in blocks and was concealed using a centralised telephone facility.
Setting: Four tertiary cardiothoracic surgery centres in England.
Participants: Patients with ischaemic heart disease with at least 50% proximal stenosis of the LAD, suitable for either PTCA or MIDCAB, and with no significant disease in another vessel.
Interventions: Patients randomised to PTCA had local anaesthetic and underwent PTCA according to the method preferred by the operator carrying out the procedure. Patients randomised to MIDCAB had general anaesthetic. The chest was opened through an 8–10-cm left anterior thoracotomy. The ribs were retracted and the left internal thoracic artery (LITA) harvested. The pericardium was opened in the line of the LAD to confirm the feasibility of operation. The distal LITA was anastomosed end-to-side to an arteriotomy in the LAD. All operators were experienced in carrying out MIDCAB.
Main outcome measures: The primary outcome measure was survival free from cardiac-related events. Relevant events were death, myocardial infarction, repeat coronary revascularisation and recurrence of symptomatic angina or clinical signs of ischaemia during an exercise tolerance test at annual follow-up. Secondary outcome measures were complications, functional outcome, disease-specific and generic quality of life, health and social services resource use and their costs.
Results: A total of 12,828 consecutive patients undergoing an angiogram were logged at participating centres from November 1999 to December 2001. Of the 1091 patients with proximal stenosis of the LAD, 127 were eligible and consented to take part; 100 were randomised and the remaining 27 consented to follow-up. All randomised participants were included in an intention-to-treat analysis of survival free from cardiac-related events, which found a non-significant benefit

from MIDCAB. Cumulative hazard rates at 12 months were estimated to be 7.1 and 9.2% for MIDCAB and PTCA, respectively. There were no important differences between MIDCAB and PTCA with respect to angina symptoms or disease-specific or generic quality of life. The total NHS procedure costs were £1648 and £946 for MIDCAB and PTCA, respectively. The costs of resources used during 1 year of follow-up were £1033 and £843, respectively.

Conclusions: The study found no evidence that MIDCAB was more effective than PTCA. The procedure costs of MIDCAB were observed to be considerably higher than those of PTCA. Given these findings, it is unlikely that MIDCAB represents a cost-effective use of resources in the reference population. Recent advances in cardiac surgery mean that surgeons now tend to carry out off-pump bypass grafting via a sternotomy instead of MIDCAB. At the same time, cardiologists are treating more patients with multi-vessel disease by PTCA. Future primary research should focus on this comparison. Other small trials of PTCA versus MIDCAB have now finished and a more conclusive answer to the original objective could be provided by a systematic review.

Contents

List of abbreviations

AMIST	Angioplasty versus Minimally Invasive Surgery Trial
CABG	coronary artery bypass grafting
CI	confidence interval
CROQ	Coronary Revascularisation Outcome Questionnaire
DMC	Data Monitoring Committee
ECG	electrocardiogram
ETT	exercise tolerance test
IQR	inter-quartile range
ITT	intention-to-treat
LAD	left anterior descending coronary artery
LITA	left internal thoracic artery
MI	myocardial infarction
MIDCAB	minimally invasive direct coronary artery bypass
NCCHTA	National Coordinating Centre for Health Technology Assessment
OPCAB	off-pump coronary artery bypass
OR	odds ratio
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RD	risk difference
SAQ	Seattle Angina Questionnaire
SD	standard deviation
SF-36	Short Form with 36 Items

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Objectives

To compare the (a) clinical and (b) cost-effectiveness of minimally invasive direct coronary artery bypass grafting (MIDCAB) and percutaneous transluminal coronary angioplasty (PTCA) with or without stenting in patients with single-vessel disease of the left anterior descending coronary artery (LAD).

Design

Multi-centre randomised trial without blinding. The computer-generated sequence of randomised assignments was stratified by centre, allocated participants in blocks and was concealed using a centralised telephone facility.

Setting

Four tertiary cardiothoracic surgery centres in England.

Participants

Patients with ischaemic heart disease with ≥ 50% proximal stenosis of the LAD, suitable for either PTCA or MIDCAB, and with no significant disease in another vessel.

Interventions

Patients randomised to PTCA had local anaesthetic and underwent PTCA according to the method preferred by the operator carrying out the procedure.

Patients randomised to MIDCAB had general anaesthetic. The chest was opened through an 8–10-cm left anterior thoracotomy. The ribs were retracted and the left internal thoracic artery (LITA) harvested. The pericardium was opened in the line of the LAD to confirm the feasibility of operation. The distal LITA was anastomosed end-to-side to an arteriotomy in the LAD. All operators were experienced in carrying out MIDCAB.

Main outcome measures

The primary outcome measure was survival free from cardiac-related events. Relevant events were death, myocardial infarction, repeat coronary revascularisation and recurrence of symptomatic angina or clinical signs of ischaemia during an exercise tolerance test at annual follow-up. Secondary outcome measures were complications, functional outcome, disease-specific and generic quality of life, health and social services resource use and their costs.

Results

Participants were recruited from November 1999 to December 2001; 1091 of 12,828 consecutive patients undergoing a diagnostic angiogram or elective PTCA had proximal stenosis of the LAD. Of the 1091, 127 were eligible and consented to take part; 100 were randomised and the remaining 27 consented to follow-up.

All randomised participants were included in an intention-to-treat analysis of survival free from cardiac-related events, which found a non-significant benefit from MIDCAB (hazard ratio = 0.77, 95% confidence interval 0.38 to 1.57, $p = 0.47$). Cumulative rates of cardiac-related events at 12 months were estimated to be 7.1 and 9.2% for MIDCAB and PTCA, respectively. There were no important differences between MIDCAB and PTCA with respect to angina symptoms or disease-specific or generic quality of life.

The total NHS procedure costs were £1648 and £946 for MIDCAB and PTCA, respectively. The costs of resources used during 1 year of follow-up were £1033 and £843, respectively.

Conclusions

We found no evidence that MIDCAB was more effective than PTCA. However, the trial did not have sufficient power and we cannot rule out this possibility. The procedure costs of MIDCAB were considerably higher than those of PTCA. Given the small and non-significant differences in

effectiveness between MIDCAB and PTCA and the considerably higher costs of MIDCAB, it is unlikely that MIDCAB represents a cost-effective use of resources in the reference population.

Recent advances in cardiac surgery mean that surgeons now tend to carry out off-pump bypass grafting via a sternotomy instead of MIDCAB. At the same time, cardiologists are treating more patients with multi-vessel disease by PTCA. Future primary research should focus on this comparison. Other small trials of PTCA versus MIDCAB have now finished and a more conclusive answer to the original objective could be provided by a systematic review.

Chapter 1
Introduction

Background

Treatment of coronary heart disease is a very important area of healthcare to the NHS.[1] It is generally accepted that interventional treatment is indicated for proximal stenosis of the left anterior descending coronary artery (LAD). For these patients, the two main established treatment procedures are coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA), which are both effective, although PTCA is less invasive and cheaper. Both PTCA and conventional CABG [grafting the left internal thoracic artery (LITA) to the LAD] are more effective than medical therapy in relieving symptoms and improving survival.[2–4] An alternative procedure with equal or better effectiveness could achieve substantial savings for the NHS; savings could arise **either** because the primary procedure itself was less expensive, **or** because its improved effectiveness obviated the need for subsequent medical or surgical therapies.

In the current era, PTCA with stenting is the most widely used treatment for isolated stenosis of the LAD because the early clinical outcomes after PTCA are similar to those after CABG and PTCA has relatively low cost and patients recover rapidly. However, the main drawback of PTCA is the risk of restenosis. Up to 30% of patients who undergo PTCA may suffer a recurrence of their symptoms within 1 year, many of whom require a further intervention with increased requirements for repeat angiography, PTCA or CABG surgery. However, like surgery, the techniques and materials used for PTCA are evolving with continuing improvements in outcome, for example, angioplasty with and without stenting and different types of stent.[5,6] In addition to this problem, the outcome for certain types of lesion (type C) may be worse after PTCA.[7]

Minimally invasive direct coronary artery bypass

In recent years, minimally invasive direct coronary artery bypass (MIDCAB) grafting has been developed for treating patients with proximal stenosis of the LAD.[8–10] This operation involves a small left anterior thoracotomy and anastomosis of the LITA to the LAD by direct suture.[8–10] It is performed either on the beating heart with the use of stabilising devices or using a minimal access bypass system with endo-aortic clamping and cardioplegic arrest (Heartport Inc., USA).[11] It appears increasingly accepted that, although complex minimally invasive bypass systems may be crucial to the development of more complex intracardiac operations, single-vessel revascularisation of the LAD can be performed in experienced hands on the beating heart without cardiopulmonary bypass.

Preliminary case series[8,9,12] indicate that MIDCAB is safe, relatively cheap and less invasive than CABG, and potentially more effective than PTCA. Peri-operative complications (mortality, 0.6%; re-operation, 1.2%[8]) are less frequent than with CABG, and of a similar frequency to angioplasty. However, given the sample size of existing case series, this aspect of the technique needs to be investigated carefully as experience increases. In ~5% of patients, the MIDCAB technique may be deemed unsuitable, and the procedure has to be converted to a standard procedure.[8,9] MIDCAB appears to give good anastomotic patency, relief of symptoms and short hospital stays with the promise of a long-lasting result based on the known longevity of LITA grafting after conventional CABG surgery.[8,9]

The promising results from case series using MIDCAB[8,9,12] demonstrate the need for a formal evaluation to compare the effectiveness and cost-effectiveness of current practice, that is, PTCA, with MIDCAB. Preliminary data from the single prospective observational study indicate that the risk of re-intervention after MIDCAB is much lower than after PTCA.[12] Therefore, there is a clear case for a randomised controlled trial (RCT) of the clinical and cost-effectiveness of MIDCAB versus PTCA for the treatment of isolated stenosis of the LAD.

Objectives

The objectives of the study were to compare the (a) clinical effectiveness and (b) cost-effectiveness

of MIDCAB and PTCA with stenting, if appropriate, in patients with single vessel disease of the LAD using an RCT study design. We hypothesised that MIDCAB would have better clinical effectiveness than PTCA with respect to survival free from cardiac-related events 1 year after treatment.

Chapter 2
Methods

Participating centres

The Angioplasty versus Minimally Invasive Surgery Trial (AMIST) was carried out in several centres. Six cardiac centres agreed to take part when the study was planned:

- United Bristol Healthcare NHS Trust, Bristol Royal Infirmary (Bristol)
- Glenfield NHS Trust, Leicester (Leicester)
- Central Manchester Health NHS Trust, Manchester Royal Infirmary (Manchester)
- St Mary's NHS Trust, St Mary's Hospital, London (London)
- Papworth Hospital NHS Trust, Cambridge (Papworth)
- Leeds NHS Trust, Leeds General Infirmary (Leeds).

Bristol was the coordinating centre for the study. At least one surgeon in each of the centres had substantial experience of MIDCAB. When AMIST started recruiting, all centres performed at least 750 PTCA procedures per year.

Study population

The reference study population was all patients with proximal stenosis of the LAD, suitable for either PTCA or MIDCAB, with no significant disease in any other vessel. Patients were recruited from those undergoing a diagnostic angiogram or elective PTCA.

Eligibility criteria

The suitability of patients for PTCA dictated the selection criteria (below), and the lesion had to be judged technically suitable for PTCA by at least one senior operator:

1. There had to be evidence of ischaemia, either by exercise test or isotope perfusion scan (except for patients with unstable angina, in whom there should be ECG changes during exercise).
2. The lesion had to be at least 50% diameter stenosis (or 75% cross-sectional area) by visual assessment or quantitative coronary angiography.
3. The lesion had to lie in the proximal half of the LAD.
4. There had to be a significant segment of normal vessel (at least twice the vessel diameter) lying between the lesion and the distal left main coronary artery.
5. The lesion should not involve or compromise a major graftable side branch.
6. Anterograde flow through the lesion had to be demonstrable.

Both elective and 'urgent', but not emergency, patients were eligible. Emergency patients were defined as those for whom an intervention was required within 24 hours. Urgent patients included those with unstable angina. Urgent patients were included because they constitute a large proportion of PTCA patients (up to 50%), and are suitable for either PTCA or MIDCAB. Patients who required emergency intervention within 24 hours of angiogram were excluded from the study. All inclusion and exclusion criteria are summarised in *Table 1*.

The eligibility of elective patients was determined from the usual clinical investigations, for example, exercise tolerance test (ETT) or diagnostic angiography. The eligibility of urgent patients was determined at angiography following admission. For urgent patients, PTCA or MIDCAB was carried out during the same admission.

Reliability of the application of the eligibility criteria was estimated by comparing the judgements of a cardiologist and cardiac surgeon, who independently reviewed the angiograms of the first 100 patients who were believed to have proximal stenosis of the LAD.

Target sample size with justification

The primary outcome was the rate of event-free survival at 12 months. The proportion of patients undergoing PTCA and MIDCAB expected to experience a cardiac-related event or death in the first year after the procedure was uncertain when the study was designed. One recent paper had indicated that 14 ± 9% of patients undergoing angioplasty with stenting suffer a cardiac-related clinical event or a recurrence of angina within 1 year,[13] but larger studies had reported failure

TABLE 1 *Summary of inclusion and exclusion criteria*

Inclusion criteria	Exclusion criteria
A significant segment of normal vessel (at least double the vessel diameter) lies between the lesion and the distal left main coronary artery	Aortic/mitral regurgitation, grade III/IV
Certainty that the lesion does not involve or compromise a major graftable side branch	Body mass index >34
LAD lesion has stenosis at least 50% diameter (or 75% cross-sectional area) by visual assessment or quantitative coronary angiography	Disease in a major coronary vessel other than the LAD requiring intervention
Lesion lies in the proximal half of the LAD	Evidence of severe thoracic disease or bullous emphysema on chest X-ray or history of chronic obstructive pulmonary disease as indicated by forced expiratory volume <40%
Patient has a lesion of the LAD (left anterior descending) that is suitable for angioplasty	History of pericarditis, median sternotomy, thoracotomy, chest irradiation or pleurodesis
Patient has angina	Known bleeding diathesis
Patient shows clinical evidence of ischaemia	Left ventricular impairment (angiogram or echocardiography indicating ejection fraction <30%)
There is demonstrable anterograde flow through the lesion	Malignant hypertension necessitating hospitalisation, or systolic blood pressure >240 mmHg within the previous 30 days
	Marfan's syndrome or related connective tissue disorder
	Patient participating in another research study
	Patient unable to comply with the requirements of the protocol
	Previous CABG
	Previous PTCA/stent in the proximal LAD
	Symptomatic cerebrovascular disease
	Significant stenotic valve disease
	Transmural MI during the past month
	Uncontrolled diabetes as indicated by more than three serum glucose concentrations >350 mg/dl within the previous 7 days

rates of 20 ± 4%.[5,14] Case series of patients who had undergone MIDCAB had reported recurrence of symptoms in 3 ± 4%[10] and 8 ± 4% of patients.[9]

On the basis of the literature, we suggested that plausible expected risks of events were 6% for MIDCAB and 16% for angioplasty with stenting after 1 year of follow-up. We proposed that the study should be designed to detect a difference in the rate of recurrence of symptoms of 10%. *Table 2* shows the sample sizes (5% significance level, two-tailed and for both 80 and 90% power) required to detect a 10% difference in the risk of an event for different absolute levels of risk for MIDCAB and PTCA, assuming an analysis comparing the number of events observed in the two groups. On the basis of these calculations, we set a target sample size of 360. This sample size would have allowed the study to detect a standardised difference in continuous outcomes [symptom and quality of life (QoL) scores] of 0.3 with 80% power at a 5% (two-tailed) significance level.

TABLE 2 *Sample sizes required to detect a 10% difference in the risk of an adverse event for different levels of baseline risk and power*

PTCA vs MIDCAB	80% power	90% power
18 vs 8%	350	470
16 vs 6%	330	440
14 vs 4%	250	340

The sample sizes shown in *Table 2* are based on 'risk' analyses. At the outset, we planned that trial

data about cardiac-related events would be analysed by survival methods, allowing periods of follow-up longer than 1 year to be included. Using survival analysis means that the trial would have had slightly greater power than indicated for the given sample sizes.

Recruitment and randomised assignment

Recruitment

In each centre, a log was kept on a daily basis documenting the demographic and clinical characteristics of all patients undergoing an angiogram (hospital number, gender, date of birth, ethnicity and diagnoses). These logs were maintained by the research nurses. Patients diagnosed with single vessel disease of the LAD were initially assessed against the eligibility criteria for the trial by the research nurse. If a patient appeared to be eligible after this assessment, a cardiologist checked the angiographic eligibility criteria and, if in the cardiologist's opinion the patient satisfied these criteria, eligibility was checked with one of the surgeons experienced in carrying out MIDCAB.

Patients considered eligible by both a cardiologist and a cardiac surgeon were given the Patient Information Sheet and received an explanation of the trial from the cardiologist or surgeon. At least 24 hours usually elapsed between patients receiving the Patient Information Sheet and being asked to consent, but this was not always possible for urgent patients.

Information about the study was given to urgent patients after they had had their angiograms and their consent to be randomised was sought shortly afterwards; for these patients, PTCA or MIDCAB was carried out during the same admission. This arrangement was not ideal, since it required urgent patients to make a decision about joining the study quickly and at a time when they were likely to be anxious because of their clinical condition. However, we believed that it was important to include urgent patients to make the findings of the trial more applicable and we presented the case for doing so in our applications to a Multi-centre and Local Research Ethics Committees.

Patients were asked to sign two copies of the consent form. One copy was given to the patient and the other was filed with the patient's medical records. Both copies were also signed by either a cardiologist or cardiac surgeon. Once the consent form had been signed, the treatment allocation for the patient was obtained by telephoning the automated randomisation facility at the coordinating centre.

The consent forms allowed patients to consent to randomisation and follow-up separately. If an eligible patient did not consent to being randomised, he or she was asked to consent to being followed up in the same way as randomised patients (see 'Data collection procedures', p. 7). Once a patient had signed the consent form (either for randomisation and follow-up, or for follow-up only), a letter was sent to the patient's GP to notify him or her that the patient had agreed to participate in AMIST.

Randomised assignment

The sequence of randomised assignments for the trial was generated in advance by computer. The sequence was stratified by centre and allocated participants in blocks of unequal length (block lengths of two, four, six and eight; varied block length was used to preserve masking of treatment allocation, since the trial was not blinded) to balance the numbers in the two arms of the trial better than would be expected with simple randomisation. The assignments were held in a computer which participating centres accessed by telephone. Study numbers, dates of calls and the interventions allocated were recorded by the computer software.

Allocation was concealed by virtue of the assignments being held in the computer. The assignments could not be viewed. Assignments were disclosed strictly in accordance with the predetermined sequence for each centre and the next assignment was only disclosed in response to a telephone call to the central randomisation facility.

Generation of the sequence of randomised assignments for the trial was implemented by the company that provided the central telephone randomisation facility. Participants were enrolled by study nurses and clinicians in each centre as described above.

Patients who agreed to be followed up but who did not consent to randomisation were not registered on the central telephone randomisation facility. Instead, centres telephoned the trial coordinator in Bristol for an identification number for a patient.

Every effort was made by centres to carry out the intervention that was assigned to a patient within 1 month.

Description of interventions

Percutaneous transluminal coronary angioplasty (PTCA)

Patients randomised to PTCA were given a local anaesthetic and PTCA was carried out according to the method preferred by the operator carrying out the procedure. At the outset, the use of stenting in conjunction with PTCA was a crucial consideration in view of evidence that stenting improves the outcomes of PTCA.[5,13,14] At the same time, cardiologists felt that it was important to recognise that stenting is not clinically necessary for a minority of patients. It was therefore agreed that cardiologists would use stents for all patients for whom they judged stenting was required. Clinical indications for stenting were identified under three main headings:

- 'Bail out': the need for stenting arises from severe disruption of the vessel lumen compromising flow at the time of the procedure.
- Sub-optimal result: the need for stenting arises because of significant residual stenosis, filling defect, asymmetry of the lesion or impairment of flow, despite there being no signs of ischaemia during the procedure.
- Elective stent: the characteristics of the lesion (large plaque, eccentric lesion, long lesion, etc.) merit a decision to stent before the first dilatation.

Clinical indications for leaving a patient without a stent were also identified, i.e. no residual stenosis, filling defect or irregularity on a check angiogram taken at least 5 minutes after the wire has been removed.

All patients undergoing PTCA received the following medications:

- ticlopidine 250 mg twice daily, to start 48 hours before PTCA, if possible, and for 4 weeks following PTCA
- aspirin 150–300 mg daily, continuing for the patient's lifetime unless contraindications develop
- heparin during the procedure only, using a titrated dose to maintain a 300-second clotting time.

Patency of the vessel was assessed by angiography after the procedure was completed.

Minimally invasive direct coronary artery bypass graft (MIDCAB)

Patients randomised to MIDCAB were operated on using the following procedure. Under general anaesthesia, the chest was opened through an 8–10-cm incision in the fourth or fifth intercostal space. The ribs were retracted and the LITA harvested, either under direct vision or using thoracoscopic assistance. The pericardium was then opened in the line of the LAD to confirm the feasibility of the operation via limited access.

The patient was systemically heparinised (1 mg/kg), the coronary artery immobilised and blood flow controlled by placing encircling snares proximally and distally. The distal LITA was then anastomosed end to side to an arteriotomy in the LAD. After completing the anastomosis, the heparin was reversed with protamine and the chest closed in layers, leaving a single drain within it.

When the trial was proposed, MIDCAB had been used successfully by the lead applicant[9] and colleagues. In a series of 155 patients, patency was demonstrated in 96% immediately postoperatively and the event-free survival rate over 1 year was estimated to be 92%. Approximately 250 MIDCAB procedures had been carried out in the planned six participating centres.

Description of outcomes

The primary outcome measure was survival free from cardiac-related events, that is, a combined outcome of all-cause death or a cardiac-related event. Relevant cardiac-related events were defined as:

- myocardial infarction (confirmed by electrocardiographic findings)
- repeat revascularisation (either PTCA or cardiac surgery)
- recurrence of symptomatic angina
- recurrence of angina evidenced by findings of ischaemia during an ETT at the annual follow-up.

The following secondary outcome measures were also defined in the protocol, although the instruments used to measure these outcomes were reviewed before starting the trial (see 'Outcomes', p. 11):

- Complications of the index procedure, including the need for a further revascularisation procedure.

- Functional outcome, measured using the Seattle Angina Questionnaire (SAQ)[15,16] (a self-completion questionnaire) at 3, 6 and 12 months after the index intervention, and by an ETT using the Bruce protocol at 12 months. Standard features of the ETT were documented, that is, exercise duration, time to onset of angina pain and time to 1-mm segment depression in any given lead.
- Generic QoL, measured using the General Well-being Index[17,18] and the EuroQol/EQ5D[19,20] (self-completion questionnaires) at 3, 6 and 12 months. The General Well-being Index had been used previously to assess anxiety and depression in patients with cardiovascular disease.[21] The EuroQol was included because it provides a QoL utility measure.

Data describing the use of health and social services, including all secondary/tertiary care, investigations subsequent to discharge following the index procedure, contacts with GPs and other members of the primary care team and care in the home given by social services, prescribed medications and the associated costs of these resources were also collected for the economic evaluation (see 'Economic evaluation', p. 9).

Previous studies of this kind have often used patency of the treated vessel at follow-up as an outcome measure, for example, angiography. We did not assess patency at 1 year because (a) patency is not the primary concern of patients, (b) angiography has a high cost (at least £500 per patient when the trial was designed) and (c) we had ethical concerns about requiring asymptomatic patients to undergo angiography, which carries a small risk of morbidity and mortality.

Blinding

It will be clear from the descriptions of the interventions (see 'Description of interventions', p. 6) that neither the surgeons and cardiologists providing the interventions nor the patients could be blinded. For example, one intervention required a general anaesthetic and involved a chest wound (MIDCAB) and the other required a local anaesthetic and involved a groin wound (PTCA).

However, we proposed to blind the assessment of the primary outcome, that is, the occurrence of cardiac-related events, and to ask a cardiologist and a cardiac surgeon to carry out independent 'adjudication' of possible cardiac-related events. Unfortunately, it quickly became clear that it was not possible to blind outcome assessment (see 'Outcomes', p. 11).

In order to obtain informed consent from participants, it was necessary to describe the aim of the study and the nature of the two interventions being compared. Therefore, patients also were not blind to the treatment allocation when they completed questionnaire outcomes.

All potential adverse events were also sent to the cardiologist and a cardiac surgeon for independent review.

Data collection procedures

Demographic and clinical details of participants were recorded on a standard form when they were recruited to the study; these details included date of birth, gender, ETT and angiography findings, medications, and whether or not a patient was hypertensive or diabetic. ETTs were assessed preoperatively, as part of the normal clinical practice prior to MIDCAB or PTCA.

Procedural details, including complications (death in hospital, myocardial infarction, arrhythmias, bleeding, transfusion, wound infection or inflammation, postprocedural persistent angina, taken to operating theatre after the index procedure), deviations from the planned procedure (including conversions to surgery from PTCA or conversion from MIDCAB to conventional CABG) and theatre/catheter laboratory resources used were documented at the time of the index procedure. Other hospital resources used during admission for the index procedure were also recorded.

Patients collected data about their use of health and social services in monthly 'diaries'. The research nurse in each centre collected the information monthly either by a telephone call (months 1, 2, 4, 5 and 7–11) or by sending a questionnaire to patients for them to complete (months 3, 6 and 12, coinciding with the collection of functional and QoL data).

The SAQ and other QoL questionnaires were completed by patients before undergoing their assigned procedures and at 3, 6 and 12 months. The questionnaires were printed as a single A4 booklet and were sent to patients with a covering letter, enclosing a prepaid reply envelope. The front page stated the patient's name and study ID number. If a patient did not return the booklet

within 10 days of sending it out, the research nurse telephoned to make sure that the patient had received it. If the booklet had not been received, the nurse sent another one with a covering letter and prepaid reply envelope. If a patient returned the booklet but had missed some of the questions, the research nurse called the patient to try to obtain the missing information. If a patient did not return the booklet within 7 days of sending the reminder (or within days of the reminder telephone contact), the research nurse telephoned again and, if possible, collected the information requested in the booklet over the telephone.

During follow-up, adverse events were documented from clinical records and by contacting patients and, if necessary, their GPs. Research staff were alerted to the occurrence of adverse events from healthcare contacts recorded in patients' diaries.

ETTs were carried out at 1 year for event-free patients whenever this was possible. Some patients had requested to withdraw from further follow-up by this time and, for some patients, 1 year had not elapsed from the time of the index procedure when data collection ceased.

Research nurses continued to follow up patients who had survived the first year following their procedures without experiencing an event by sending a short questionnaire every 3 months requesting information about hospital admissions, recurrence of angina symptoms or other major disease events.

We originally proposed that all patients experiencing a recurrence of symptoms should be reassessed angiographically when they are re-referred, as part of their normal clinical management. Unfortunately, it was not always possible to ensure that an angiogram was carried out in these circumstances (see 'Outcomes', p. 11).

Research governance

The study was approved by the South West Multi-centre Research Ethics Committee on 14 May 1999 (ref. MREC/99/6/24).

A Data Monitoring Committee (DMC) was established at the start of the trial and first met on 3 March 2000. The DMC consisted of:

- Mr Stephen Evans, Consultant Cardiologist, Trelisk Hospital, Truro, Cornwall
- Mr Bruce Keogh, Consultant Cardiothoracic Surgeon of University Hospital Birmingham (Chairman)
- Dr Barnaby Reeves, Senior Lecturer in Epidemiology, London School of Hygiene and Tropical Medicine and co-investigator with the Angioplasty versus Minimally Invasive Surgery Trial (AMIST)
- Dr Robert West, Reader in Epidemiology, University of Wales College of Medicine
- Mr Ian White, Lecturer in Medical Statistics, London School of Hygiene and Tropical Medicine.

Although Dr Reeves was a co-investigator, he was not involved in the data collection for AMIST and attended the DMC meeting in order to provide any additional information about the trial that other members of the DMC might require. He did not participate in decisions made by the DMC.

One interim analysis was planned. The DMC defined the following rule for stopping AMIST on the basis of the interim analysis:

> "The trial will be stopped if a difference between groups is observed in a single, planned interim analysis with respect to the primary outcome at a significance level of $p < 0.001$; the interim analysis should be carried out approximately 3 months after 50% of the target sample size has been recruited (giving a median follow-up of about 6 months for the first 50% of recruited patients)."

The DMC concluded that the date of the interim analysis could not be set at the outset because of uncertainty about the recruitment rate.

Statistical analyses

Reliability of the application of the eligibility criteria and the adjudication of cardiac-related events (see 'Outcomes', p. 11) was estimated using Cohen's kappa statistic (κ).[22]

For the primary outcome, that is, survival free from death or a cardiac-related event, Cox proportional hazards analyses were carried out, entering into the model only the variable describing the intervention. The date of entry was the date of randomisation. The date of censoring for patients who did not experience any cardiac-related event and who survived to the end of the trial was either 30 June 2002 for patients who had not reached 1 year of follow-up or the date of last known follow-up (i.e. date of last 3-month follow-up form completed) for patients who had been

TABLE 3 *Costs of 'work-up' tests and medications at the time of admission*

	PTCA: mean (SD) (£)	MIDCAB: mean (SD) (£)	Difference (95% CI) (£)	*p*-Value
Tests	58.64 (11.79)	58.48 (8.91)	0.16 (–4.02 to 4.34)	0.94
Medications at admission	43.99 (24.46)	38.53 (22.00)	5.46 (–3.85 to 14.77)	0.25

followed up for more than 1 year. Patients who died or who experienced a cardiac-related event did not contribute survival time after the date of the first event. Cumulative hazard estimate graphs are presented for the first 2 years of follow-up only.[23]

Regression modelling was used to analyse other data on effectiveness, that is, the SAQ and other QoL instruments, adjusting estimates of differences between groups for baseline scores. Regression diagnostic tests were inspected. The use of multiple regression assumes that QoL scores are parametric, an assumption which is usually made for data from the instruments that were used. The potential for increasing precision of estimates of differences between groups was a further justification for using regression.

Intention-to-treat (ITT) analyses were carried out for all outcomes. A secondary analysis of the primary outcome was also carried out according to the treatment received, including non-randomised patients (in which the date of 'entry' was set to be the date of the intervention) but excluding two patients who did not receive either intervention.

Statistical significance was set at 5% (two-tailed) for all inferential tests.

Economic evaluation

The economic assessments were based on data that were collected on the resources used in MIDCAB and PTCA procedures. These included the length of stay on wards in total and after the procedure, drugs prescribed at admission, discharge and after discharge, theatre time of staff and equipment used in procedures and health and social services resources used by patients during follow-up.

These resources were costed using data collected from the Bristol Royal Infirmary, Personal Social Services Research Unit data on staff costs, formulary costs of prescriptions from the *British National Formulary* (www.bnf.org.uk) and costing data for tests from laboratories. Data were also collected on travel costs and out-of-pocket expenses of patients and the number of days that patients and carers had to take off work; a cost was imputed to this time using average wage rates recorded in the New Earnings Survey.[24] Economic data are often highly skewed, which may limit the validity of conventional statistical methods used to derive point estimates and confidence intervals (CIs), especially when sample sizes are small. To overcome this disadvantage, sensitivity analysis was undertaken to assess the robustness of the findings, whereby costs were varied by ±10–50%. In addition, calculations were made to assess the changes required to create equivalence in costs between the two procedures for the key variables.

Cost data on tests used as part of the standard work-up and medications on admission were excluded from the final analysis, as they should not differ between the two treatment arms. This assumption was borne out by the data (see *Table 3*) that showed no significant difference in these costs for the two treatment arms.

Chapter 3

Deviations from the protocol

Participating centres

The original proposal submitted by Bristol included three centres, namely Bristol, Leicester and Manchester, and proposed to recruit participants over a period of 2 years. The NHS R&D National Coordinating Centre for Health Technology Assessment (NCCHTA) (the commissioning body) requested that the proposal should be revised to incorporate a competitive bid which also included three centres, namely Papworth, London and Leeds, and to shorten the recruitment period to 1 year. London was recruited to the trial after a delay of a few months. Discussions with Papworth and Leeds continued for some months but they eventually declined to take part in the trial.

Recruitment period

Participants were recruited from November 1999 to December 2001. Bristol, Leicester and Manchester started recruiting at the same time but there were delays in setting up the trial in London; for example, recruiting a research nurse took 4 months and recruitment started there only in May 2000.

Bristol and Leicester recruited participants over a 2-year period and London and Manchester recruited for 1 year only. This difference in recruitment period occurred because of negotiations with the NCCHTA about continuing the trial in view of the non-participation of Papworth and Leeds and the slow rate of recruitment in the other centres. After 1 year, we proposed to focus the effort of research staff on the two centres that were recruiting relatively well, Bristol and Leicester, since it was difficult to justify the investment in the research nurses in Manchester and London given their rates of recruitment.

Outcomes

Contrary to our intention, it was not possible to blind data reported to the coordinating centre about potential adverse and cardiac-related events. The inability to blind arose because information from centres about suspected events was not always presented in a uniform manner and often disclosed information about the intervention, for example, 'anastomosis patent'. We were faced with two alternatives: either extract the information from reports about suspected events so that the information could be presented without disclosing the intervention received or present the information as it had been submitted by centres, accepting that the reviewers would not be blinded. Because the process of data extraction itself could not be blinded, and because one reviewer was a surgeon and one a cardiologist (i.e. representing potentially opposing interests), we chose to present the information as it had been submitted. The reliability of classification of all suspected events was described using Cohen's κ statistic.[22]

Evidence available for review was not always the same for all patients suspected of having experienced a cardiac-related event. Centres tended to re-investigate patients suspected of having a recurrence of angina according to their usual practices, rather than according to the protocol. We obtained all available information when a participant was reinvestigated and presented this to the cardiologist and cardiac surgeon, who independently adjudicated possible cardiac related events. Reviewers were allowed to conclude that there was insufficient information to decide whether or not an event had occurred, in which case we requested additional information and, if available, fed back the information to the reviewers. A third opinion was obtained in the few instances of disagreement.

It was also sometimes impossible to obtain an ETT at 12 months. Some patients declined to provide information during follow-up, including having an ETT. Because recruitment continued to within 6 months of the end of data collection, the last recruited patients had also not reached 12 months' follow-up.

Further discussion of the most appropriate outcomes for the trial led us to substitute the Short Form with 36 Items (SF-36)[25] for the Well-being Index as our chosen measure of generic QoL. We also included a newly developed

questionnaire, the Coronary Revascularisation Outcome Questionnaire (CROQ),[26,27] as a measure of disease-specific QoL. The CROQ was developed to provide an instrument for assessing the outcome of both PTCA and CABG interventions for coronary revascularisation. It includes items from the SF-36 and the SAQ but also includes other questions covering cognitive and psychological domains. The CROQ has been evaluated and validated for patients undergoing PTCA and CABG but not for patients undergoing MIDCAB.

Sample size and statistical analyses

AMIST recruited a much smaller than expected sample size, partly because some centres withdrew and partly because recruitment was slower than expected even in centres that recruited relatively well. The small sample size impacted on the proposed analyses in two ways:

1. At the outset, we proposed to investigate whether effectiveness depended on the date when a procedure was carried out, since PTCA and MIDCAB techniques might have altered during the course of the study. This subgroup analysis was not carried out.
2. We recruited both randomised and non-randomised participants to AMIST. We had planned to carry out a comprehensive cohort analysis,[28] assuming that we might have similar numbers of randomised and non-randomised patients, to compare the estimates of effectiveness in the two cohorts. The small number of non-randomised participants (n = 27, about one-quarter of the number of randomised participants) and the fact that almost all non-randomised participants underwent PTCA (25/27) made this analysis impracticable. Instead, for the primary outcome only, we simply carried out an explanatory (observational) analysis according to the treatment received, including all participants who received one or other intervention. Four patients, one who died before receiving the assigned intervention, two who received medical treatment only and one who underwent planned CABG as the initial procedure, were excluded from this explanatory analysis.

Research governance

After the first meeting, the DMC received information and communicated electronically. An interim analysis was not carried out because the sample size never reached half of the planned target of 360, that is, any interim analysis would have had very little power to detect a difference.

Chapter 4
Results

Recruitment and assignment to interventions

Participants were recruited from November 1999 to December 2001. Bristol and Leicester recruited over 2 years and Manchester (November 1999 to October 2000) and London (April 2000 to March 2001) recruited over only 1 year. During these periods of recruitment, the details of 12,828 consecutive patients undergoing a diagnostic angiogram or elective PTCA were logged. A total of 1091 patients (8.5%) were identified as potentially suitable for the trial (*Figure 1*), that is they were believed to have proximal stenosis of the LAD only.

The first 100 patients (out of 961; data for both reviewers available for 94) considered for the trial were evaluated independently by a cardiologist and a surgeon to test the reliability of the application of the eligibility criteria. The κ estimates were derived first for the decision about whether a patient was eligible or not and, second, for classification of patients in five categories (eligible; not eligible because of compromising a side-branch; not eligible because lesion too close to the left main stem; not eligible because the degree of stenosis was <50%; not eligible for another reason). The κ estimates were excellent in both cases, namely 0.75 ($p < 0.0001$) and 0.77 ($p < 0.0001$). The decisions of the reviewers are shown in *Table 4*.

Of the patients regarded as potentially suitable, 794 did not satisfy the eligibility criteria and 130 were not approached; reasons for being ineligible or not being approached are described in *Table 5*. Of the remaining 167 eligible patients, 40 did not consent to participate at all (24.0%). Recruitment figures by centre are shown in Appendix 1 and reasons for refusing to participate in Appendix 2.

A total of 100 participants were randomised, 50 to PTCA and 50 to MIDCAB. The baseline characteristics of the participants in the two groups are summarised in *Tables 6* and 7. There were no serious imbalances in characteristics between groups. Six randomised participants did not receive the assigned interventions. Of the 48 patients who underwent PTCA, only one did not receive a stent. The remaining 27 participants agreed to follow-up but declined to be randomised; 25 preferred and underwent PTCA, one preferred and underwent MIDCAB and one underwent conventional CABG. A flow chart for the trial is shown in *Figure 1*. Adherence to other CONSORT criteria[29] are described in Appendix 3.

Prior to receiving the intervention, diagnoses for 2/100 (2%) randomised participants were reviewed following a second angiogram and were judged to be different compared with the initial assessment and the revised diagnoses were no longer consistent with the eligibility criteria. Both participants were in the PTCA group. One was found to have insufficiently severe disease at the time of the planned index procedure, did not proceed to have PTCA and was given medical treatment. The other was found not to have a sufficiently severe LAD lesion on review of the angiogram and was given medical treatment. A third patient who elected to undergo MIDCAB but who consented to follow-up was found to have double-vessel disease and was given CABG. These patients were included in the analyses since they were initially considered to satisfy the eligibility criteria.

Time to intervention

Differential time spent waiting for the intervention is often a concern in randomised controlled trials that compare surgical and medical treatments. Although PTCA involves a procedure, we were similarly concerned that the waiting time for PTCA might be shorter than for MIDCAB despite the intention to provide both interventions to all patients with 1 month. We therefore compared the time from randomisation to intervention between groups.

Unsurprisingly, times to intervention were highly positively skewed. Twenty-two and 19 randomised participants received PTCA and MIDCAB, respectively, within 30 days. The corresponding median times to intervention were 35 days (inter-quartile range 6.5–54 days) and 44 days (inter-quartile range 14–66 days). A non-parametric rank sum test did not indicate a statistically

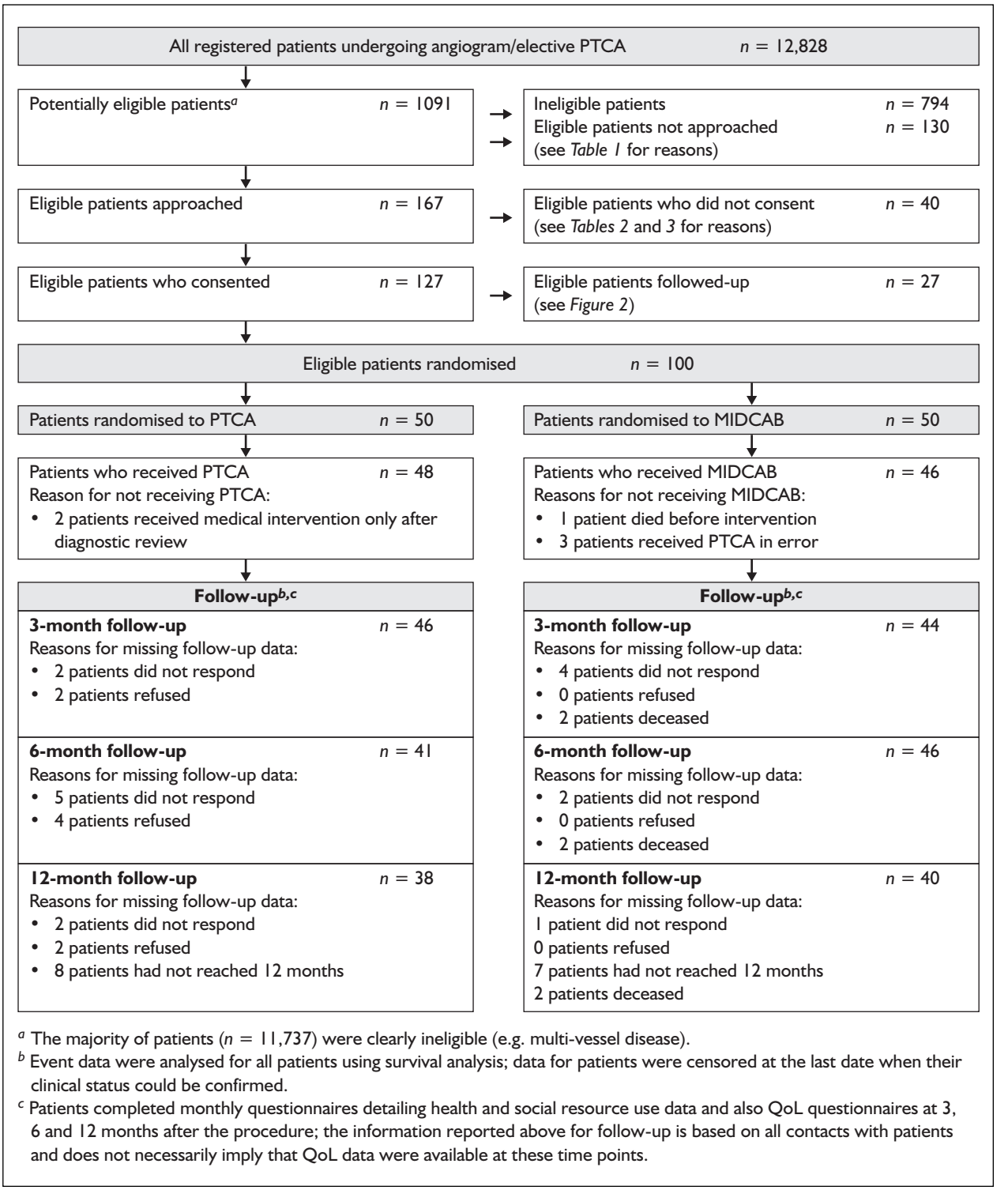

FIGURE 1 *Flow chart of recruitment and follow-up for AMIST*

significant difference between the medians ($z = -1.339$, $p = 0.18$). The analysis of times to intervention revealed one participant, randomised to PTCA, who inexplicably had a date of intervention that preceded the date of randomisation.

Short-term outcomes

There were no conversions to surgery (either to MIDCAB or to CABG) among participants randomly assigned to PTCA. There were three conversions from MIDCAB to median sternotomy

TABLE 4 *Agreement between independent reviewers (one cardiologist and one cardiac surgeon) in applying the eligibility criteria: (a) with respect to overall eligibility and (b) with respect to five main classification categories*

(a)

	Decision of cardiac surgeon		Total
Decision of cardiologist	**Not eligible**	**Eligible**	
Not eligible	80	3	83
Eligible	2	9	11
Total	82	12	94

$\kappa = 0.75$, $p < 0.0001$.

(b)

	Decision of cardiac surgeon					Total
Decision of cardiologist	**(i)**	**(ii)**	**(iii)**	**(iv)**	**(v)**	
(i) Not eligible – lesion compromises side branch	26	0	0	6	1	33
(ii) Not eligible – lesion too close to left main stent (LMS)	0	8	1	1	0	10
(iii) Not eligible – stenosis <50%	0	0	14	1	0	15
(iv) Not eligible – other reason	0	0	2	21	2	25
(v) Eligible	0	0	1	1	9	11
Total	26	8	18	30	12	94

$\kappa = 0.77$, $p < 0.0001$.

among participants randomly assigned to MIDCAB, one of which was planned before starting the operation because of the patient's body structure. The non-randomised patient who underwent conventional CABG did not represent a conversion since he was found to have double-vessel disease on review, received two grafts and there was no record of an incision for a thoracotomy having been made initially.

Table 8 summarises the frequencies of complications/adverse events that occurred in hospital. No major adverse events occurred. *Table 9* summarises the duration of length of stay overall, in recovery and in intensive care. Not surprisingly, there were statistically significant differences between the medians for the two groups with respect to total, postprocedure and intensive care length of stay (all $p < 0.0001$).

Duration of follow-up

For randomised patients, 12-month follow-up was complete for 84/100 (84%) patients. The median follow-up for cardiac-related events was 20.5 months (inter-quartile range 14.8–24.2 months). For those who refused randomisation, 22/27 (81%) completed 12-month follow-up and the median follow-up for cardiac-related events was 20.9 months (inter-quartile range 15.0–22.4 months). There was no difference in the duration of follow-up between groups for randomised patients (difference in mean follow-up (MIDCAB – PTCA) = 0.3 months, 95% CI –2.5 to 3.0, $p = 0.84$). Duration of follow-up for non-randomised patients was not compared between groups because there was only one who underwent MIDCAB.

Survival free from cardiac-related events

Reliability of classification of cardiac-related events

Table 10 shows the classifications of suspected cardiac-related events by the independent cardiologist and cardiac surgeon. The reliability of classification was moderate ($\kappa = 0.59$). Reliability appears worse than it really was because some disagreements were easily reconciled. The three misclassified but confirmed events related to:

- One patient whose ETT showed evidence of an MI; the disagreement arose because the cardiac surgeon wanted confirmation that the ECG changes had not been present at the time the patient was recruited.
- One patient who definitely had recurrent angina; the disagreement arose because angiography showed a lesion in a different vessel.

TABLE 5 *Reasons for excluding patients from AMIST*

Reason (excluding patient refusals)	Bristol (*n* = 146)	Leicester (*n* = 461)	London (*n* = 203)	Manchester (*n* = 114)	Total (*n* = 924)
Aortic/mitral regurgitation, III–IV	2	8	2		12 (1%)
Bleeding diathesis	1	1	2		4 (0%)
Blocked LAD	26	109	7	26	168 (18%)
Body mass index ≥ 35 (severe obesity)	2	6		2	10 (1%)
Bullous emphysema		2	1		3 (0%)
Disease not severe enough for intervention		16		6	22 (2%)
Doctor refused or forgot AMIST	2	33	62	3	100 (11%)
Doctor refused, took patient off waiting list		26		2	28 (3%)
Emergency case	5	19	3	11	38 (4%)
Previous cardiac history[a]	3	5	2		10 (1%)
Lesion involved side branch	36	28	3	22	89 (11%)
Left ventricular impairment (ejection fraction <30%)	2	7	1	1	11 (1%)
Lesion was in the distal part of the LAD	6	11	11	5	33 (3%)
Lesion not 50% of diameter stenosis	12	81	25	12	130 (13%)
No ischaemia	2	9	3	9	23 (2%)
Disease in other major coronary vessels	1		18		19 (2%)
Previous CABG	1	4	7	1	13 (1%)
Previous MI	13	7	34	4	58 (6%)
Previous PTCA/stent	8	36	12	2	58 (6%)
Patient in another study		5	1		6 (1%)
Patient unable to comply		2			2 (0%)
Patient unable to speak English	1		2		3 (0%)
Significant stenotic valve disease	1	6		2	9 (1%)
Surgeon/surgical bed unavailable		8			8 (1%)
Symptomatic cerebrovascular disease	2	3			5 (1%)
Too close to the left main stem	11	11	3	2	27 (3%)
Thrombus	1		2		3 (0%)
Unsuitable for PTCA/MIDCAB	7	11	2	3	23 (2%)
Other, e.g. aneurysm[b]	1	7		1	9 (1%)

[a] Pericarditis/median sternotomy/thoracotomy/chest irradiation/pleurodesis.
[b] Bristol, uncontrolled diabetes; Leicester, missed cases (2), lesion long/complex (3), patient too young (1), aneurysm (1); Manchester, referred to another hospital.

TABLE 6 *Baseline demographic and clinical characteristics of PTCA and MIDCAB groups*

Baseline characteristic	PTCA (n = 50)[a]		MIDCAB (n = 50)[b]	
	n/median	%/IQR	*n*/median	%/IQR
Age (years)	54.5	48.9–61.4	58.8	53.2–66.6
Female	7	14	15	30
Non-Caucasian	2	4	1	2
Employment status:[a]				
Full-time or part-time work	22	49	19	40
Home-maker	4	9	1	2
Retired	11	24	22	46
Disabled	5	11	3	6
Unemployed	3	7	3	6
New York Heart Association class:[b]				
1	6	14	7	14
2	20	45	35	70
3	16	36	7	14
4	2	5	1	2
Unstable angina[c]	9	20	10	20
Degree of stenosis of LAD:[d]				
≥ 50% and < 80%	7	15	11	23
≥ 80% and < 90%	9	20	11	23
≥ 90% and < 95%	15	33	12	25
≥ 95%	15	33	14	29

[a] Missing for five PTCA and two MIDCAB participants.
[b] Missing for six PTCA participants.
[c] Missing for five PTCA and one MIDCAB participants.
[d] Missing for four PTCA and two MIDCAB participants.

TABLE 7 *Baseline functional and quality of life characteristics of PTCA and MIDCAB groups*

Baseline characteristic	PTCA (n = 50)		MIDCAB (n = 50)	
	Median	SD	Median	SD
SAQ:[a]				
Physical limitation	56.1	21.7	57.7	20.2
Angina stability	42.6	28.0	32.8	28.3
Angina frequency	51.6	25.2	53.6	25.5
Treatment satisfaction	87.5	13.1	87.8	14.1
Disease perception	41.7	20.6	40.1	16.5
CROQ:[b]				
Core total	50.1	5.4	50.7	5.8
Symptoms	56.2	23.6	56.6	23.3
Physical	59.3	27.4	60.6	25.8
Cognitive	76.5	23.2	73.6	26.2
Psychological	62.5	19.4	66.3	18.1
SF-36:[c]				
PCS	29.5	12.7	28.9	13.6
MCS	44.2	9.9	46.1	11.4
EuroQol:[d]				
Utility score	0.66	0.26	0.72	0.22
Health status score	57.3	19.8	64.4	17.4

[a] Scores could not be calculated because of missing data for six PTCA and five MIDCAB participants.
[b] Scores could not be calculated because of missing data for two PTCA and four MIDCAB participants.
[c] Scores could not be calculated because of missing data for five PTCA and eight MIDCAB participants.
[d] Scores could not be calculated because of missing data for two PTCA and three MIDCAB participants.

TABLE 8 *Short-term complications/adverse events in PTCA and MIDCAB groups*

	PTCA (n = 49)[a]		MIDCAB (n = 49)[b]	
Decision of cardiologist	***n***	**%**	***n***	**%**
Death in hospital	0	0	0	0
Conversion to surgery/sternotomy	0	0	3	6
Myocardial infarction	0	0	0	0
Ventricular fibrillation	0	0	1	2
Bleeding femoral puncture	5	10	0	0
Arrhythmia	0	0	4	8
Postprocedure persistent angina	1	2	0	0
Postprocedure taken to operating theatre:				
Because of bleeding	0	0	1	2
Because of infection	0	0	0	0
Because of sternotomy	0	0	0	0
Transfusion requirement (patients):				
Blood	0	0	1	2
Platelets	1	2	1	2
Fresh frozen plasma	0	0	1	2
Wound infection	1	2	3	6
Wound inflammation	1	2	0	0
Pericarditis	0	0	2	4

[a] One patient assigned to PTCA is excluded because the patient was treated medically and never received a date for PTCA. A second patient, who attended for PTCA and underwent an angiogram but who did not undergo PTCA because the degree of stenosis of the lesion was judged to be <50% at the time of the planned intervention, is included.
[b] One patient assigned to MIDCAB is excluded because the patient died at home before undergoing the planned operation.

TABLE 9 *Length of stay and use of blood products in PTCA and MIDCAB groups*

	PTCA (n = 49)[a]		MIDCAB (n = 49)[b]	
Decision of cardiologist	**Median**	**IQR[c]**	**Median**	**IQR[c]**
Total stay (days)	2	1–3	6	5–8
Postprocedure stay (days)	1	1–1	4	4–5
Time in recovery (hours)	0	0–0.83	0	0–1
Time in intensive care unit (hours)	0	0–0	5	0–20

[a] One patient assigned to PTCA is excluded because the patient was treated medically and never received a date for PTCA. A second patient, who attended for PTCA and underwent an angiogram but who did not undergo PTCA because the degree of stenosis of the lesion was judged to be <50% at the time of the planned intervention, is included.
[b] One patient assigned to MIDCAB is excluded because the patient died at home before undergoing the planned operation.
[c] IQR, inter-quartile range.

TABLE 10 *Agreement between independent reviewers (one cardiologist and one cardiac surgeon) in classifying non-fatal suspected events*[a]

	Decision of cardiac surgeon			Total
Decision of cardiologist	**No event**	**Event**	**Uncertain**	
No event	12 (0)	3 (2)	3 (0)	18 (2)
Event	1 (1)	13 (13)	0 (0)	14 (14)
Uncertain	2 (0)	0 (0)	2 (0)	4 (0)
Total	15 (1)	16 (15)	5 (0)	36 (16)

$\kappa = 0.59$, $p < 0.0001$.
[a] Numbers in parentheses represent suspected events that were confirmed as cardiac-related events, i.e. there were 16 non-fatal cardiac-related events in total.

TABLE 11 *Randomised participants experiencing cardiac-related events during follow-up (ITT analysis; median follow-up 20.5 months)*

	PTCA (n = 50)		MIDCAB (n = 50)	
Event	***n***	**(%)**	***n***	**(%)**
Death	0	(0)	2	(4)
MI	2	(4)	0	(0)
Re-intervention	2	(4)	0	(0)
Recurrent angina	5	(10)	4	(8)
Evidence of ischaemia at 12-month ETT	8	(16)	8	(16)
Total	17	(34)	14	(28)

- One patient whose ETT was limited in duration; the disagreement arose because of differing interpretation of the extent to which exercise was limited. The cardiologist responsible confirmed that the ETT was positive and additional anti-angina drugs were prescribed.

The two patients about whom both reviewers were uncertain were classified as agreements because both reviewers agreed that the patients had experienced an episode of pericarditis and were uncertain only about whether pericarditis should be classified as a cardiac-related event. Pericarditis was not included in our definition of cardiac-related events and these two patients are included in *Table 8*.

Primary, intention-to-treat analysis

All randomised participants were included in the primary analysis of survival free from cardiac-related events. *Table 11* shows the frequencies of events that occurred during follow-up, without taking into account time that had elapsed since the procedure. The table distinguishes re-intervention, symptomatic recurrent angina that caused participants to seek re-investigation and participants found to have evidence of ischaemia from the results of the 12-month ETT (exercise duration limited by the onset of chest pain or an ST depression >1 mm). In practice, the distinction between these categories may be artificial, arising more from access to, or the availability of, hospital resources (e.g. re-intervention versus symptomatic recurrent angina; information on the latter patients sometimes indicated that re-intervention was planned or scheduled) or from the symptom threshold of patients (e.g. symptomatic recurrent angina versus evidence of ischaemia from the ETT at 12 months) than from true differences in the types of events experienced.

Figure 2 shows the inverted Kaplan–Meier curves for survival free from cardiac-related events for the PTCA and MIDCAB groups. *Table 12* shows the observed cumulative percentage experiencing events after different durations of follow-up. The survival analysis for MIDCAB versus PTCA found a non-significant benefit from MIDCAB (hazard ratio = 0.77, 95% CI 0.38 to 1.57, $p = 0.47$). The proportional hazards assumption was satisfied ($\chi^2 = 0.00$, $p = 1.00$). The estimated cumulative percentages experiencing events at 1 year for PTCA and MIDCAB groups from the survival model were 9.2 and 7.1%, respectively.

Secondary, explanatory analysis

All participants who underwent PTCA or MIDCAB were included in a secondary analysis of survival free from cardiac-related events, excluding two patients assigned to PTCA who did not receive any intervention, one patient assigned to MIDCAB who died before receiving any intervention and one patient who elected to have surgery and who underwent CABG. *Table 13* shows the frequencies of events that occurred during follow-up, without taking into account time that had elapsed since the procedure (cf. *Table 10*).

Figure 3 shows the inverted Kaplan–Meier curves for survival free from cardiac-related events for the PTCA and MIDCAB groups, as estimated by the explanatory analysis. As with intention-to-treat analysis, the explanatory analysis found a non-significant benefit from MIDCAB (hazard ratio = 0.70, 95% CI 0.36 to 1.38, $p = 0.31$). The proportional hazards assumption was satisfied ($\chi^2 = 0.08$, $p = 0.78$). The estimated cumulative percentages experiencing events at 1 year for PTCA and MIDCAB groups from the survival model were 7.4 and 5.2%, respectively.

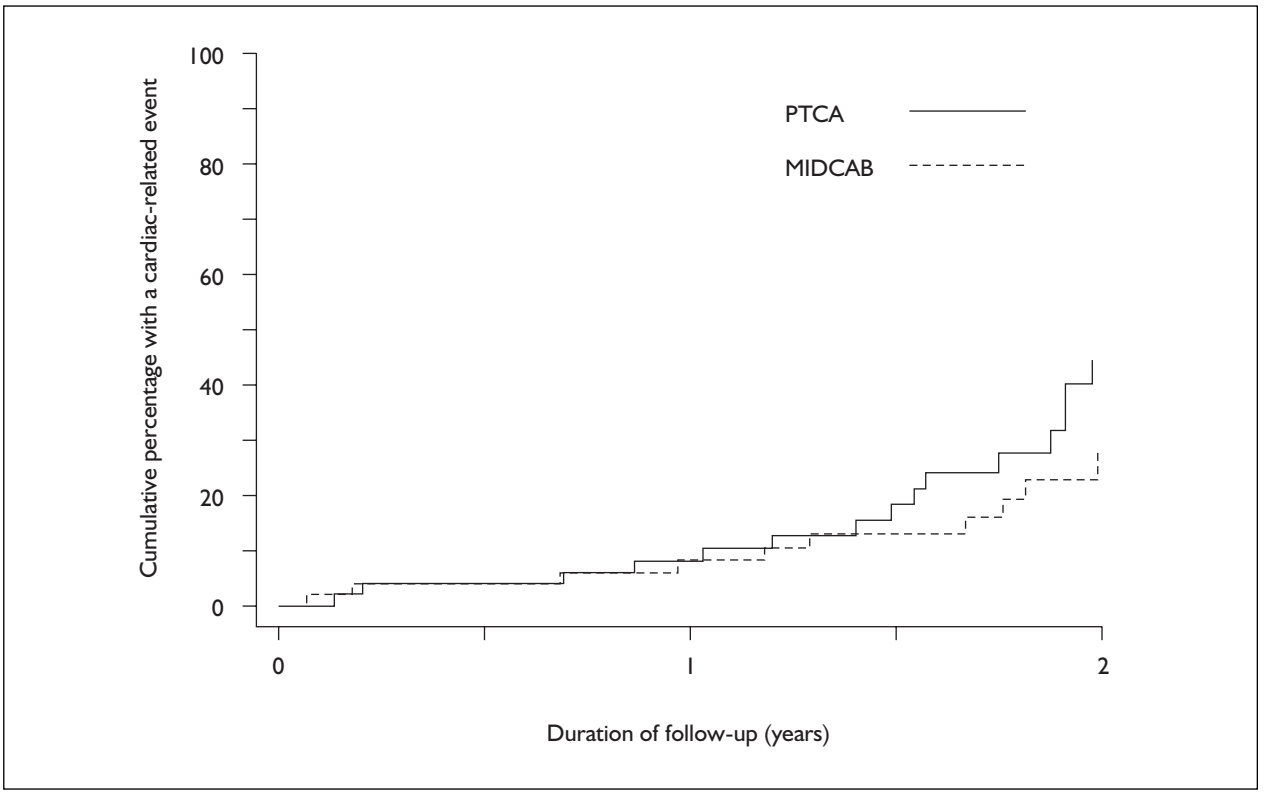

FIGURE 2 *Inverted Kaplan–Meier survival curves for PTCA and MIDCAB groups, ITT analysis*

TABLE 12 *ITT analysis: numbers at risk of experiencing cardiac-related events, and observed cumulative percentages experiencing an event, for PTCA and MIDCAB participants with increasing duration of follow-up*

Follow-up duration (months)	Number at risk	Cumulative %	95% CI
PTCA:			
6	49	4.0	0.010 to 0.151
12	44	8.1	0.031 to 0.201
18	30	18.3	0.095 to 0.337
24	14	44.5	0.330 to 0.642
MIDCAB:			
6	49	4.0	0.010 to 0.151
12	42	8.2	0.032 to 0.201
18	31	13.0	0.060 to 0.267
24	16	27.6	0.152 to 0.469

TABLE 13 *All participants experiencing cardiac-related events during follow-up (explanatory analysis)*

	PTCA (*n* = 76)		MIDCAB (*n* = 47)	
Event	***n***	**(%)**	***n***	**(%)**
Death	0	(0)	1	(2)
MI	2	(3)	0	(0)
Re-intervention	2	(3)	0	(0)
Recurrent angina	8	(11)	4	(8)
Evidence of ischaemia at 12-month ETT	13	(17)	7	(17)
Total	25	(32)	12	(27)

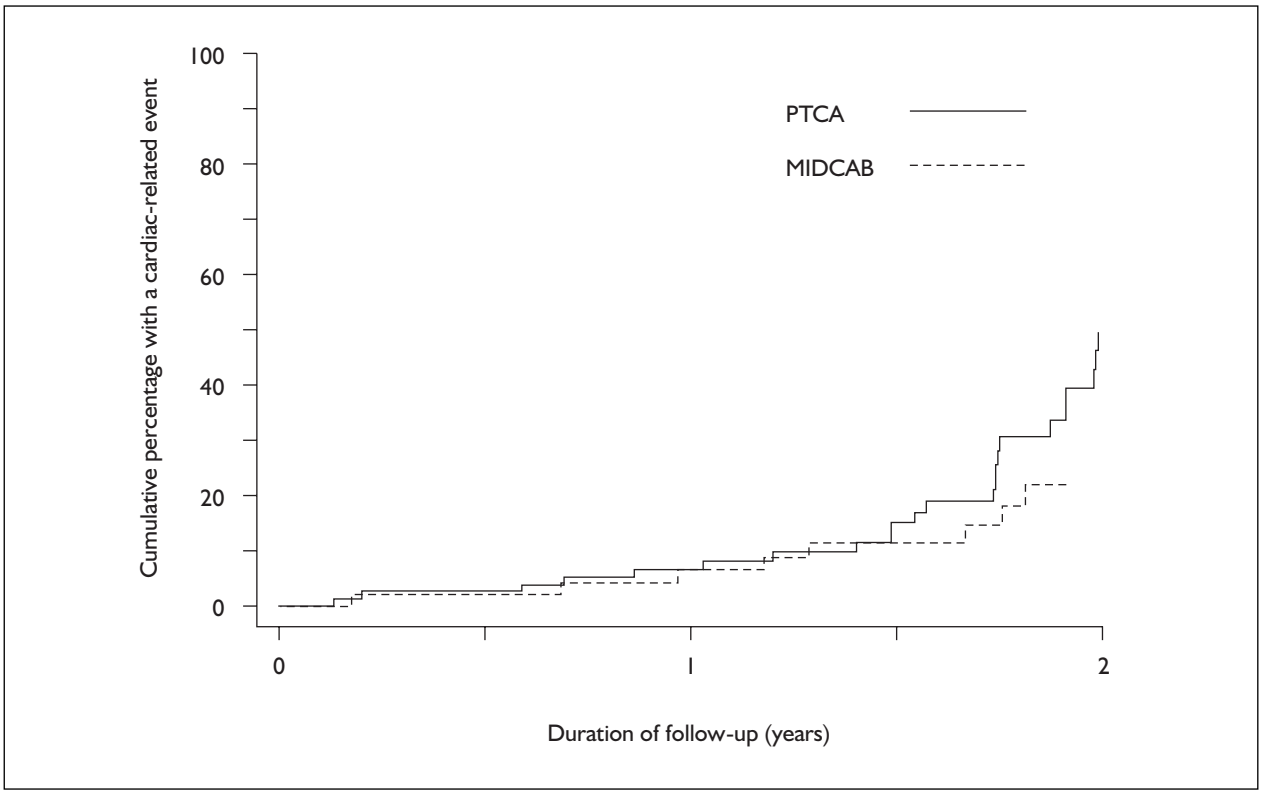

FIGURE 3 *Inverted Kaplan–Meier survival curves for PTCA and MIDCAB groups, explanatory analysis*

TABLE 14 *Explanatory analysis: numbers at risk of experiencing cardiac-related events, and observed cumulative percentages experiencing an event, for PTCA and MIDCAB participants with increasing duration of follow-up*

Follow-up duration (months)	Number at risk	Cumulative %	95% CI
PTCA:			
6	75	2.6	0.007 to 0.100
12	66	6.6	0.028 to 0.152
18	45	15.0	0.083 to 0.264
24	15	49.6	0.350 to 0.663
MIDCAB:			
6	47	2.1	0.003 to 0.139
12	41	6.5	0.021 to 0.187
18	30	13.7	0.064 to 0.280
24	16	23.8	0.129 to 0.415

Functional ability, symptoms and disease-specific quality of life

The results for the SAQ and the CROQ [means and standard deviations (SDs) for each group, mean difference and 95% CI] are shown in *Tables 15* and *16*. Differences were estimated from regression analyses that adjusted for the participants' baseline scores. Therefore, the tabulated mean differences are not equal to the differences between the tabulated means.

For both measures, differences tended to favour MIDCAB although only two differences reached statistical significance (SAQ treatment satisfaction score at 3 months, $p = 0.02$; CROQ cognitive score at 3 months, $p = 0.04$). SAQ dimensions of angina stability and frequency and CROQ physical and cognitive dimensions (especially at 3 months) suggested the most consistent benefit of MIDCAB but the differences were still statistically non-significant. Given the large number of comparisons carried out (5 + 6 dimensions/scores at three different time points), one should interpret the one or two statistically significant results with caution.

TABLE 15 *SAQ scores at 3, 6 and 12 months for PTCA and MIDCAB groups, and differences between groups*

	PTCA			MIDCAB			PTCA vs MIDCAB[a]		
	n	Mean	SD	*n*	Mean	SD	Difference	95% CI	*p*
Physical limitation:									
At 3 months	43	77.9	22.5	43	80.1	20.5	3.59	–4.78 to 12.0	0.40
At 6 months	39	76.3	24.8	46	78.6	20.3	2.62	–6.36 to 11.6	0.56
At 12 months	35	80.4	24.6	38	81.0	21.4	2.99	–6.95 to 12.9	0.55
Angina stability:									
At 3 months	45	72.8	31.0	42	82.1	24.2	11.3	–0.96 to 23.5	0.07
At 6 months	40	66.3	29.7	44	70.5	29.2	8.03	–4.34 to 20.4	0.20
At 12 months	36	64.6	28.3	36	66.7	29.9	2.31	–12.0 to 16.6	0.75
Angina frequency:									
At 3 months	45	76.4	27.4	43	84.9	19.4	8.48	–1.45 to 18.4	0.09
At 6 months	38	76.6	29.4	44	84.3	20.6	6.49	–4.49 to 17.5	0.24
At 12 months	30	80.0	24.4	38	86.3	21.4	7.23	–4.14 to 18.6	0.21
Treatment satisfaction:									
At 3 months	45	87.5	14.7	43	92.3	11.9	5.70	0.78 to 10.6	0.02
At 6 months	38	86.8	16.0	45	86.4	19.1	–0.15	–7.26 to 6.96	0.97
At 12 months	35	81.3	25.1	37	84.1	23.1	2.41	–8.98 to 13.8	0.68
Disease perception:									
At 3 months	46	68.9	23.3	43	72.3	22.9	4.66	–4.58 to 13.9	0.32
At 6 months	40	68.1	23.7	45	68.0	23.4	0.61	–9.03 to 10.2	0.90
At 12 months	35	72.6	25.2	37	71.5	23.5	–0.04	–11.8 to 11.7	1.00

[a] Mean differences between groups at each time point were estimated using regression, adjusting for participants' baseline scores (see *Table 7*). Therefore, the tabulated differences are not equal to the differences between the tabulated means.

TABLE 16 *CROQ scores at 3, 6 and 12 months for PTCA and MIDCAB groups, and differences between groups*

	PTCA			MIDCAB			PTCA vs MIDCAB[a]		
	n	Mean	SD	*n*	Mean	SD	Difference	95% CI	*p*
Core total:[b]									
At 3 months	44	49.7	7.09	44	50.0	6.40	–0.19	–2.54 to 2.15	0.87
At 6 months	39	50.3	7.52	46	50.0	6.45	–0.99	–3.59 to 1.61	0.45
At 12 months	35	50.4	8.00	39	50.1	7.34	–0.67	–4.13 to 2.79	0.70
Symptoms:									
At 3 months	44	77.6	24.2	44	85.8	16.8	6.95	–0.39 to 14.3	0.06
At 6 months	38	78.7	22.9	46	84.0	18.7	4.28	–3.67 to 12.2	0.29
At 12 months	35	82.2	22.8	39	83.7	21.9	–0.16	–9.92 to 9.60	0.97
Physical:									
At 3 months	44	80.3	25.6	43	86.2	20.3	5.86	–2.83 to 14.6	0.18
At 6 months	39	79.7	26.9	46	82.1	20.5	1.76	–7.62 to 11.1	0.71
At 12 months	35	82.2	27.3	39	83.3	22.9	0.99	–10.0 to 12.0	0.86
Cognitive:									
At 3 months	44	80.0	20.4	44	85.8	21.5	7.65	0.44 to 14.9	0.04
At 6 months	39	82.9	19.6	45	82.4	22.0	2.11	–6.21 to 10.4	0.61
At 12 months	35	82.9	21.2	39	82.7	24.9	1.19	–9.19 to 11.6	0.82
Psychology:									
At 3 months	44	77.5	19.2	44	82.4	16.5	2.41	–4.01 to 8.83	0.46
At 6 months	39	79.2	20.9	45	81.2	17.1	–0.30	–7.42 to 6.82	0.93
At 12 months	35	82.1	22.1	39	84.4	18.9	2.05	–7.27 to 11.4	0.66
Satisfaction:									
At 3 months	43	84.3	16.8	44	81.4	20.9	–2.89	–10.9 to 5.20	0.48
At 6 months	38	83.8	20.2	45	79.7	22.1	–4.11	–13.4 to 5.22	0.38
At 12 months	35	80.3	21.5	38	84.9	20.2	4.61	–5.13 to 14.3	0.35

[a] Mean differences between groups at each time point were estimated using regression, adjusting for participants' baseline scores (see *Table 7*). Therefore, the tabulated differences are not equal to the differences between the tabulated means.

[b] CROQ core total dimension is a T-score, i.e. the dimension is scored on a scale with a mean of 50 and a SD of 10.

Generic quality of life

The results for the SF-36 and the EuroQol (means and SDs for each group, mean difference and 95% CI) are shown in *Table 17*. Differences were estimated from regression analyses that adjusted for the participants' baseline scores.

For both measures, differences again tended to favour MIDCAB although the differences were very small and only one reached statistical significance (SF-36 MCS score at 12 months, $p = 0.04$). As for the SAQ and CROQ, given the number of comparisons carried out, this statistically significant result should be interpreted with caution.

Economic evaluation

Costs of PTCA and MIDCAB

The costs profiles of the two procedures differed markedly (see *Table 18*). MIDCAB had high costs of ward stay both before and after the procedures, with an average length of stay of 5 days after the operation and 7 days in total compared with 1.4 days for PCTA after the procedure and 2.7 days in total. The costs of these components were £1120 per patient for MIDCAB after the procedure and £1586 in total, and £162 per patient for PCTA after the procedure and £310 in total. (Since patients were randomised to PTCA and MIDCAB, there is no reason for the ward costs before the procedure to differ between groups. Therefore, only the ward costs after the procedure are included in the following analyses.) Not only was the length of stay longer but also the cost per day was higher, reflecting more intensive care required postoperatively. The MIDCAB cases spent an average of 25 hours in ITU but no PCTA cases were admitted to ITU. The MIDCAB cases also spent more time in recovery (32 hours in total compared with 22 hours for PCTA cases).

There were considerable consumables and equipment used in PCTA that amounted to £538 but the staff costs in operating theatre/catheter laboratory were greater for the MIDCAB at £478 compared with £143 for PCTA. Drug costs during admission and at discharge were slightly higher for PCTA; the medicines prescribed on discharge were significantly different ($p < 0.001$). The costs of medications during follow-up were also slightly higher for the PCTA group. This seems consistent with clinical experience of prescribing for this group. Follow-up costs that included consultations at home and in surgeries and telephone calls for advice were higher for MIDCAB than for PCTA.

Use of hospital facilities during follow-up was also higher for MIDCAB than for PCTA.

Furthermore, MIDCAB patients had to take a mean 2.5 days more off work. Therefore, patient costs in the reference population were also highest in the MIDCAB group.

Cost-effectiveness of MIDCAB

The utility values (derived using EuroQol) at 12 months are based on the values recorded at that time and are summarised in *Table 17*. The differences between the groups were not statistically significant after 12 months' follow-up. The mean 12-month utility scores are shown again in *Table 19*, together with the total NHS costs of PTCA and MIDCAB and the incremental cost–utility ratio for MIDCAB, which is £44,600 per (EuroQol) quality-adjusted life year (QALY). If patient costs are included, the incremental cost–utility ratio rises to £58,724 per (EuroQol) QALY. (Alternatively, the health status profile over the 12 months could have been calculated using a weighted average of the utility at 3, 6 and 12 months. However, the weighted 12-month utility gave mean values that were almost identical with those observed at the 12-month follow-up and the estimated difference between groups, adjusted for baseline utility scores, was 0.01.)

Sensitivity analysis

Sensitivity analysis of the costs of PTCA and MIDCAB, as described in 'Economic evaluation' (see p. 9), is shown in *Table 20*. The costs of PCTA were 67% (£1789/£2681) of those for MIDCAB. The key component of this difference in costs relates to ward costs; for PCTA these were only 14% (£162/£1120) of the MIDCAB costs. Most of the difference in ward costs related to length of stay. A decrease in MIDCAB length of stay by 80% would have been needed to achieve equivalence in cost of length of stay between the procedures.

For one MIDCAB one could produce 1.4 PTCAs. There is some discussion in the literature about the possibility of the two procedures breaking even after 5 years because of the greater propensity for patients who undergo PTCA to require a repeat revascularisation procedure (either PTCA or CABG). The long-term cost-effectiveness could be modelled once reliable data on long term outcomes become available. Data already published[30,31] suggest that the rates of cardiac-related events observed in AMIST (and consequent resource use and costs during follow-up) may not be typical (see 'Findings of the study in the context of existing literature', p. 29).

TABLE 17 *SF-36 T scores (physical and mental health dimensions, PCS and MCS, respectively)[a] and EuroQol/EQ5D utility and health status scores at 3, 6 and 12 months for PTCA and MIDCAB groups, and differences between groups*

	PTCA			MIDCAB			PTCA vs MIDCAB[b]		
	n	Mean	SD	*n*	Mean	SD	Difference	95% CI	*p*
SF-36 PCS:									
At 3 months	43	37.9	14.3	43	40.9	11.5	1.57	–3.40 to 6.54	0.53
At 6 months	41	37.4	15.9	45	38.0	10.8	0.01	–5.14 to 5.15	1.00
At 12 months	38	37.7	15.0	38	39.4	14.4	0.63	–5.47 to 7.03	0.80
SF-36 MCS:									
At 3 months	43	50.5	12.2	43	51.5	9.55	0.07	–4.28 to 4.42	0.98
At 6 months	41	51.1	11.2	45	52.4	10.1	1.76	–2.26 to 5.77	0.39
At 12 months	38	51.4	11.6	38	55.0	9.18	4.80	0.34 to 9.27	0.04
EQ5D utility:									
At 3 months	43	0.79	0.24	41	0.84	0.14	0.02	–0.06 to 0.10	0.60
At 6 months	39	0.78	0.24	43	0.80	0.19	–0.01	–0.10 to 0.08	0.79
At 12 months	38	0.77	0.25	40	0.82	0.22	0.02	–0.08 to 0.12	0.71
EQ5D health status:									
At 3 months	45	72.4	18.3	44	79.8	17.4	4.28	–1.94 to 10.5	0.18
At 6 months	40	74.3	20.0	46	79.7	13.8	1.07	–5.15 to 7.29	0.73
At 12 months	38	74.6	21.7	40	81.7	12.7	3.19	–4.75 to 11.1	0.43

[a] Quality of life dimension scored on a scale with a mean of 50 and a SD of 10. T scores are also normalised for the SF-36 component summaries (PCS and MCS; i.e. 50 represents the mean for a normal population).

[b] Mean differences between groups at each time point were estimated using regression, adjusting for participants' baseline scores (see *Table 7*). Therefore, the tabulated differences are not equal to the differences between the tabulated means.

TABLE 18 *Component costs per patient (£) for PTCA and MIDCAB*

Procedure costs	PTCA	MIDCAB	Ratio (PCTA/MIDCAB)	Ratio (MIDCAB/PCTA)
Hospital costs for index procedure				
Ward costs (total)	310	1586	0.20	5.12
Ward costs (postop.)	162	1120	0.14	6.91
Medication inpatient	39.8	13.4	2.97	0.34
Medication on discharge	63	37	1.70	0.59
Total medications	102.8	50.4	2.04	0.49
Procedure costs: staff	143	478	0.30	3.34
Procedure costs: equipment	538			
Total procedure costs	681	478	1.42	0.70
Total hospital costs	1093.8	2114.4	0.52	1.93
Total hospital costs postprocedure	945.8	1648.4	0.57	1.74
Hospital cost of follow-up				
Use of hospital call services	4.82	23.51	0.21	4.88
Outpatient consultations: consultants and other professionals	51.7	43.1	1.20	0.83
Accident and emergency attendances	7.84	9.64	0.81	1.23
Readmissions	297.03	393.5	0.75	1.32
Home visits by hospital staff	7.41	57.64	0.13	7.78
Total follow-up costs to hospital	368.8	527.39	0.70	1.43
Primary care				
Consultation with GP in surgery	199.13	266.43	0.75	1.34
Consultations with GP at home	5.12	13.49	0.38	2.63
Medications during follow-up	236	196	1.20	0.83
Consultations/calls to surgery	34.26	29.26	1.17	0.85
Total follow-up costs to primary care	474.51	505.18	0.94	1.06
Patients' costs				
Travel	2.76	2.2	1.25	0.80
Out-of-pocket expenses	5.46	4.82	1.13	0.88
Total patient costs during follow-up	8.22	7.02	1.17	0.85
Value of time off work				
Patients	1204.6	1498.1	0.80	1.24
Carers	41.19	32.36	1.27	0.79
Total costs of time off work	1262.23	1544.5	0.82	1.22

TABLE 19 *Estimation of incremental cost–utility for MIDCAB*

	Total cost (£)	12-month utility	Incremental cost (£)	Incremental effect	Incremental cost–utility ratio (£)
PTCA	1789	0.77	n/a		
MIDCAB	2681	0.82	892	0.02	44,600

TABLE 20 *Sensitivity analysis for costs of PTCA and MIDCAB*

Procedure costs	PCTA minus est. × 0.50	MIDCAB est. × 0.50	PCTA est. × 0.90	MIDCAB est. × 0.90	PCTA estimate	MIDCAB estimate	PCTA est. × 1.10	MIDCAB est. × 1.10	PCTA est. × 1.50	MIDCAB plus est. × 1.50
Hospital										
Ward costs (total)	155.00	793.00	279.00	1427.40	**310.00**	**1586.00**	341.00	1744.60	465.00	2379.00
Ward costs (postop.)	81.00	560.00	145.80	1008.00	**162.00**	**1120.00**	178.20	1232.00	243.00	1680.00
Medications	51.40	25.20	92.52	45.36	**102.80**	**50.40**	113.08	55.44	154.20	75.60
Procedure costs	340.50	239.00	612.90	430.20	**681.00**	**478.00**	749.10	525.80	1021.50	717.00
Total hospital costs	546.90	1057.20	984.42	1902.96	**1093.80**	**2114.40**	1203.18	2325.84	1640.70	3171.60
Total postprocedure costs	472.90	824.20	851.22	1483.56	**945.80**	**1648.40**	1040.38	1813.24	1418.70	2472.60
Follow-up costs										
Hospital follow-up	184.40	263.70	331.92	474.65	**368.80**	**527.39**	405.68	580.13	553.20	791.09
Medications during follow-up	118.00	98.00	212.40	176.40	**236.00**	**196.00**	259.60	215.60	354.00	294.00
Primary care	119.26	154.59	214.66	278.26	**238.51**	**309.18**	262.36	340.10	357.77	463.77
Total NHS costs										
Total healthcare costs	968.555	1573.49	1743.4	2832.27	**1937.11**	**3146.97**	2130.82	3461.67	2905.67	4720.46
Total postprocedure costs	894.555	1340.49	1610.2	2412.87	**1789.11**	**2680.97**	1968.02	2949.07	2683.67	4021.46
Patients' costs										
Value patients' time	602.30	749.05	1084.14	1348.29	**1204.60**	**1498.10**	1325.06	1647.91	1806.90	2247.15
Value carers' time	20.60	16.18	37.07	29.12	**41.19**	**32.36**	45.31	35.60	61.79	48.54

The bold columns show the 'best estimate' costs as found in the economic evaluation.

Chapter 5
Discussion

Summary of main findings

Recruitment to AMIST was much slower than expected and achieved only about 30% of the target sample size, partly because some centres withdrew. The trial therefore had far lower power than desired to detect the target difference in the frequency of cardiac-related events of 10% and all comparisons between PTCA and MIDCAB are imprecise. In terms of the proportion of eligible patients recruited and the multi-centre nature of the trial, we believe that the findings of the trial should be applicable to the reference population.

Survival analyses of the primary outcome (survival free from cardiac-related events) suggested a modest, but non-significant, benefit of MIDCAB. The hazard ratio decreased slightly, indicating greater benefit, in a secondary explanatory (non-randomised) analysis. Functional and QoL scores also suggested a slight benefit of MIDCAB, insomuch as the comparisons consistently favoured MIDCAB, although the size of the differences was small and almost always non-significant.

Compliance with the assigned intervention was reasonably good for randomised patients. There were no serious complications arising from either treatment and the only deaths that occurred in the study were unrelated to the interventions.

The economic evaluation suggests that PTCA is more cost-effective than MIDCAB in the treatment of proximal stenosis of the LAD provided that there is no evidence in the future, from longer term follow-up or other studies, that the additional costs of MIDCAB yield an additional health utility.

Findings of the study in the context of existing literature

The cardiac-related event rate of 7.1% at 1 year in the MIDCAB group, estimated from the survival analysis, was about the same as we expected when we calculated the target sample size for AMIST. However, the estimated cardiac-related event rate for PTCA at 1 year was only 9.2%, that is, a difference in survival free from cardiac-related events of only 2% rather than the projected 10%.

Since AMIST started to recruit, two other small RCTs of MIDCAB versus PTCA in patients with stenosis of the proximal LAD have been published, one carried out in Germany[30] and the other in Poland.[31] Both found that MIDCAB reduced the risk of cardiac-related events compared with PTCA by an amount that just reached statistical significance.

Diegeler and colleagues observed event rates at 6 months of 31.5 and 14.8% for PTCA and MIDCAB, respectively (risk difference 16.7%, 95% CI 5.6 to 27.7%).[30] These researchers had a potentially stricter definition of cardiac-related events than we did, since they did not include recurrent angina as an event but did include re-intervention on the LAD. However, in some countries, where re-intervention is likely to be carried out more quickly, re-intervention and recurrent angina may be strongly correlated. We have no explanation for their very much higher event rates.

Cisowski and colleagues observed event rates, defined as re-stenosis of and re-intervention on the target vessel, at 6 months of 12 and 2% for PTCA and MIDCAB, respectively (risk difference 10.0%, 95% CI 0.2 to 19.8%).[31] No other events, such as deaths or myocardial infarctions (MIs), were reported. These event rates are closer to those observed in AMIST, although the MIDCAB rate is considerably lower.

Figure 4 shows odds ratio (OR) and risk difference (RD) forest plots and pooled estimates for fixed-effect meta-analyses of these three RCTs. The pooled estimates (OR = 0.43, 95% CI 0.25 to 0.72; RD = 0.13, 95% CI 0.05 to 0.20) suggest a statistically significant and clinically important benefit of MIDCAB. There was no statistical evidence of heterogeneity between the studies. The pooled risk difference estimate is consistent with our hypothesised difference in effectiveness between MIDCAB and PTCA.

The other trials did not report utility data.[30,31] However, the results of the meta-analysis can be

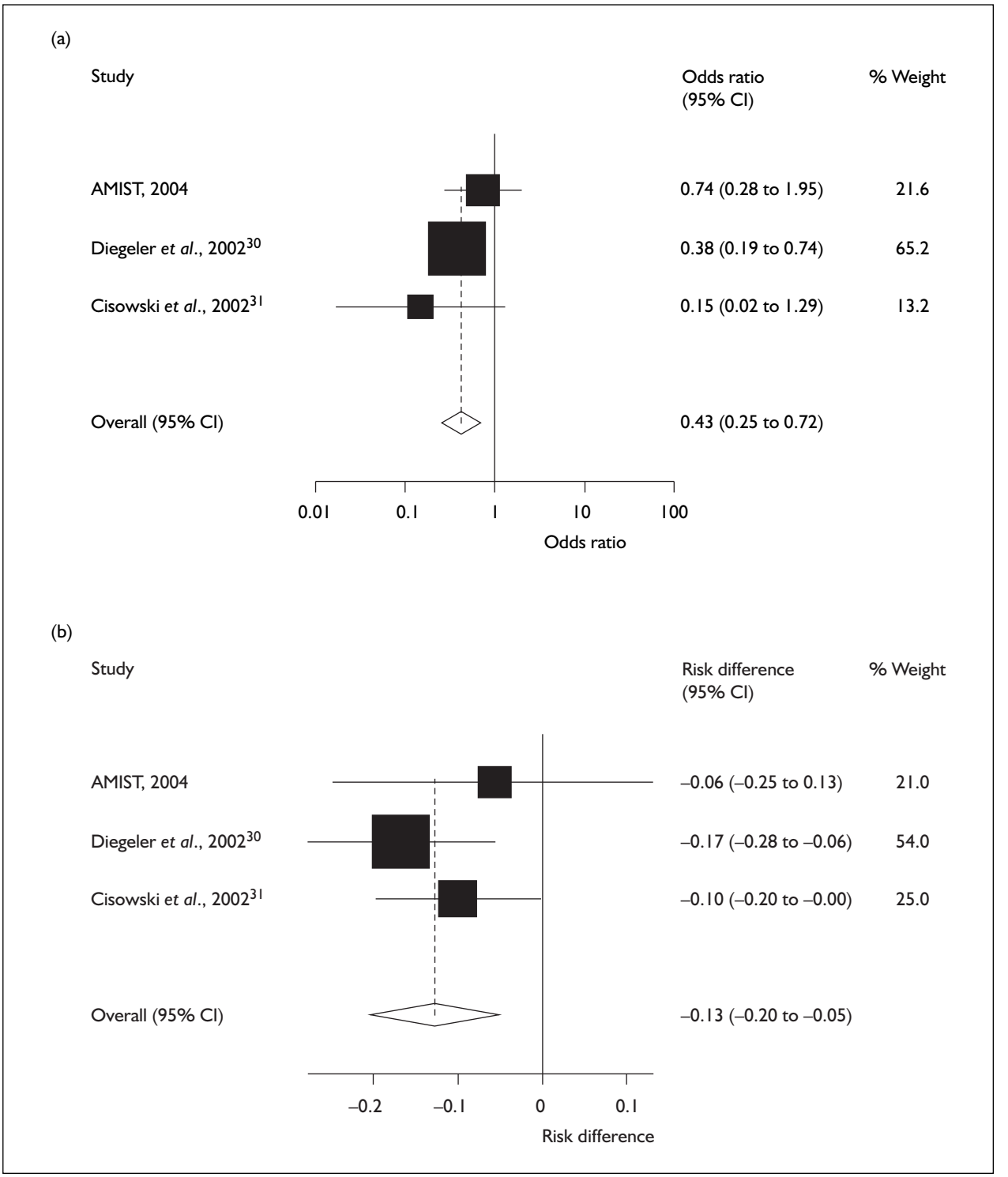

FIGURE 4 *Fixed-effect meta-analyses with (a) odds ratio and (b) risk difference measures of effect*

used for a further sensitivity analysis of the cost-effectiveness of MIDCAB versus PTCA, using cardiac-related events rather than utility as the measure of effectiveness. The estimated pooled risk difference of 13% leads to an ICER of £6862 per cardiac-related event avoided. Alternatively, our hypothesised risk difference (10%) leads to an ICER of £8920 per cardiac-related event avoided. These ICERs are clearly more favourable for MIDCAB than the one based only on data from AMIST.

Consideration of alternative explanations for the findings

Regrettably, the much smaller than expected sample size means that the finding of no difference between MIDCAB and PTCA could have arisen **either** because there is truly no difference between the interventions **or** because the study had insufficient power to detect the target difference of 10%. In other words, even if the underlying difference in cardiac-related event rate was 10%, with only 100 randomised patients the study was unlikely to detect a significant difference.

Other sources of potential bias are confounding factors and the unblinded nature of the outcome assessment. Randomisation was concealed so there should have been no opportunity for selection bias. One participant assigned to PTCA appeared to have been randomised after the intervention had taken place. This patient was retained in the analysis; if this observation truly arose because of subversion, the selection bias would have favoured PTCA. It is possible that there may have been imbalances between groups by chance, because of the small sample size, but these are taken into account by tests of statistical inference. All randomised patients were included in the analysis of survival free from cardiac-related events so loss to follow-up could not cause selection bias. The same was not true for analyses of SAQ, CROQ, SF-36 and EuroQol scores, where the proportion of randomised participants for whom responses were available dropped to about 75% at 12 months. However, non-response was similar in both groups and, at 12 months, was partly attributable to the fact that 12 months had not elapsed from the time of the intervention for the most recently recruited patients.

As described, assessment of the outcomes could not be blinded. However, the primary outcome was assessed independently by two reviewers and their reliability in classifying suspected events was described. Reliability was moderate and there was no evidence of differential bias so, at the very worst, this method of adjudicating events might have biased our estimate of effectiveness towards the null hypothesis, i.e. no difference between MIDCAB and PTCA.

With respect to the economic evaluation, the costs do not include hospital capital costs or overheads. These may well have been substantial given the difference in the intensity of service use and the prolonged use of hospital stay for the MIDCAB. Other cost data also need to be interpreted with caution. In an attempt to provide data that can be readily accessed by other researchers, we used data from the Personal Social Services Research Unit for staffing costs and data from the *British National Formulary* for drugs. The costs of stents and other materials were provided by the Bristol Royal infirmary. The costs of a bed day excluding drugs, investigations and theatre costs were also derived from data provided by the Bristol Royal Infirmary. Economic research to refine the cost measurements is continuing. Nevertheless, the sensitivity analysis suggests that the conclusion is robust to considerable variations in costs.

Difficulties in recruiting patients

The target sample size was based on three centres recruiting for 2 years (original proposal) or six centres recruiting for 1 year (revised proposal). Recruitment started in Bristol, Leicester and Manchester in November/December 1999. St Mary's in London started to recruit in May 2000. Papworth and Leeds declined to participate after initial discussions on the revised proposal, without giving reasons. Manchester and St Mary's in London stopped recruiting after 1 year because their rates of recruitment (11 and five patients, respectively) did not justify the investment required for the data collection infrastructure in these hospitals.

The total number of participants was less than 30% of the target sample size. A slower than projected recruitment rate was inevitable given the smaller than planned number of participating centres. However, the rate of recruitment was also much lower than projected in Bristol and Leicester (and even lower in Manchester and St Mary's). The trial recruited 60% of patients confirmed as eligible. Therefore, the low rate of recruitment appears to have arisen primarily because of the larger than expected proportion of patients with proximal stenosis of the LAD who were ineligible. We do not have an explanation for the large number of patients considered to be ineligible but note that 130 eligible patients were not approached because the cardiologist responsible for the patient refused or forgot to recruit them.

With hindsight, it might have been better to pay centres a fixed sum per patient recruited, thereby creating a financial incentive to recruit. However, it would have been difficult for participating centres to invest in a reliable recruitment and data collection infrastructure without the guarantee of funding.

Recommendations for further research

We have two types of recommendations as a result of the trial. The first relates to future evaluation of the cost-effectiveness of alternative strategies for coronary revascularisation, given that techniques are evolving rapidly in both interventional cardiology and cardiac surgery. The second relates to the possibility of carrying out secondary research to answer the objective addressed by AMIST.

Future primary evaluations of the cost-effectiveness of alternative strategies for coronary revascularisation

The small number of patients considered eligible for the trial leads us to question the future of MIDCAB. Since some patients not suitable for PTCA might still benefit from MIDCAB, the total number of MIDCAB operations carried out in a tertiary cardiac surgery centre in the UK would be likely to be greater than the number of participants recruited to the trial per centre per year (about 20 in Bristol and Leicester). Nevertheless, the total number of suitable patients is unlikely to be more than about 40 per centre per year in UK cardiac centres such as Bristol and Leicester. This number barely reaches the 'critical mass' required to maintain surgeons' technical expertise in what is a technically difficult operation. Increasingly, surgeons are using off-pump coronary artery bypass (OPCAB) for patients who might otherwise have undergone MIDCAB. OPCAB, which is more effective in the short-term and as effective as conventional CABG in the mid-term,[32] achieves many of the benefits of MIDCAB but is technically easier and has greater flexibility.[33] Hence MIDCAB may represent an 'evolutionary dead end'.

Cardiologists, who are effectively the 'gate-keepers' to most cardiac surgeons, regard PTCA as the treatment of preference for proximal stenosis of the LAD. Part of the difficulty in recruiting to AMIST may be attributed to their reluctance to refer such patients to cardiac surgeons if, in their opinion, they can be treated by PTCA. This difficulty in recruiting participants to RCTs of interventional cardiology versus cardiac surgery problem may become worse since, with innovations in the technology for PTCA, interventional cardiologists now treat some patients with multi-vessel disease.

Our recommendations are as follows:

- Future evaluations comparing PTCA and cardiac surgery should focus on comparing the most up-to-date PTCA technique with OPCAB rather than MIDCAB.
- Such evaluations should include all categories of patient considered suitable for PTCA, with stratification of randomisation by key patient subgroup, such as single/double-vessel disease.
- Commissioners of research should consider whether a combined strategy, that is, PTCA for one lesion and minimally invasive surgery for another, represents a plausibly cost-effective alternative to PTCA or surgery alone.
- Commissioners of research need to consider how to overcome the key difficulty of recruiting patients to evaluations comparing interventional cardiology and cardiac surgery, given the current gate-keeping arrangements.

Secondary research to compare the effectiveness and cost-effectiveness of PTCA versus MIDCAB

Through professional networks, we are aware of other RCTs of PTCA versus MIDCAB, in addition to those described above (see 'Findings of the study in the context of existing literature', p. 29). However, we believe that our own trial is currently the only one to have included an economic evaluation. Most of these trials have struggled to recruit patients, as we did, and the data for at least two groups remain unpublished. One research group stopped recruiting because they were convinced that, whatever the result of their trial might be, it would be impossible to change cardiologists' preferences for treating patients with single-vessel disease. This assertion can only be tested by quantifying more precisely the relative effectiveness and cost-effectiveness of PTCA and MIDCAB and presenting the evidence to cardiologists.

There is clearly a need for a systematic review and meta-analysis, if appropriate, of the existing trials. The meta-analysis described above, which only used published trials, may be subject to publication bias and is, to our knowledge, incomplete. It should therefore be repeated, ideally using individual patient data, following a systematic search for additional trials.

Our recommendations are as follows:

- A systematic review and meta-analysis, if appropriate, of existing trials should be carried out, ideally using individual patient data.
- The cost-effectiveness of MIDCAB should be recalculated, applying the resource and cost

data from AMIST to the pooled estimate of effectiveness determined from the systematic review.

Conclusions

We found no evidence from AMIST that MIDCAB is more effective than PTCA. MIDCAB was clearly a more expensive procedure. Given the small and non-significant differences in effectiveness between MIDCAB and PTCA and the considerably higher costs of MIDCAB, it is unlikely that MIDCAB represents a cost-effective use of resources in the reference population. Our main caution in interpreting these findings arises from the small sample size; a real difference in effectiveness of the size hypothesised may exist but the trial had insufficient power to detect it. There were few complications with either intervention.

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Contribution of authors

Fiona Taylor (Public Health Specialist) was the original research associate on the project. Harpreet Seehra (Clinical Trials Co-ordinator) and Lucy Culliford (Clinical Trials Co-ordinator) contributed to the collection and checking of the data, and reviewing the report. Gianni Angelini (Professor of Cardiac Surgery) and Alan Bryan (Consultant Cardiac Surgeon) conceived the study and also contributed to the report, as above. Barnaby Reeves (Senior Lecturer in Epidemiology) helped to design the study, analysed the data and drafted the report. Jennifer Roberts (Professor of Economics and Public Health) and Paul Jacklin (Research Fellow in Health Economics) carried at the economic evaluation and contributed to the report. Key cardiac surgeons and cardiologists from the other participating centres [Bernard Clarke (Consultant Cardiologist), Tim Cripps (Consultant Cardiologist), Rodney Foale (Consultant Cardiologist), Daniel Keenan (Consultant Cardiothoracic Surgeon), Derek Rowlands (Consultant Cardiologist), Niles Samani (Professor of Cardiology), Tomasz Spyt (Consultant Cardiac Surgeon) and Rex Stanbridge (Consultant Cardiac Surgeon)] facilitated the execution of AMIST in their own centres, recruited patients, commented on and approved this final report.

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Appendix 1

Recruitment figures by centre

Centre	Weeks recruiting	Throughput	Patients with proximal stenosis of the LAD	Patients eligible for recruitment	Eligible patients			Patients not eligible for recruitment	Patients randomised of total throughput
					Refusals	Patients not randomised but agreed to follow-up	Patients recruited and randomised		
Bristol	104	2814	209/2814 7%	63/209 30%	14/63 22%	9/63 14%	40/63 63%	146/209 70%	40/2814 1.4%
Leicester	104	6493	529/6493 8%	68/529 13%	16/68 23%	8/68 13%	44/68 64%	461/529 87%	44/6493 0.7%
London	50	1829	214/1829 12%	11/214 5%	6/11 55%	0/11% 0%	5/11 45%	203/214 95%	5/1829 0.3%
Manchester	52	1692	139/1692 8%	25/141 18%	4/25 16%	10/25 40%	11/25 44%	114/139 82%	11/1692 0.7%
Total	310	12828	1091/12828 9%	167/1091 15%	40/167 24%	27/167 16%	100/167 60%	924/1091 85%	100/12828 0.8%

Appendix 2

Reasons given by patients for refusing to participate or to be randomised

Reasons given for refusing	Total number of patients refusing	
	To participate (n = 40)	To be randomised (n = 27)
No reason given	11	3
No reason obtained/research nurse forgot	2	
Doctor rejected randomisation	2	1
Did not like idea of study	3	1
Lost confidence in the NHS	1	1
Only wants surgery (refusing PTCA)	3	2
Only wants PTCA (refusing surgery)	11	12
Could not wait for date of MIDCAB	5	5
Patient taken off waiting list	1	1
Patient sought other medical advice	1	1

Appendix 3

CONSORT checklist of items when reporting a randomised controlled trial[29]

Section and topic	Item	Details of AMIST relevant to the item
Title and abstract	1	The study is described as a randomised trial in both the title and the Executive Summary
Introduction		
Background	2	The Introduction to the report describes the scientific background and rationale for the study (pp. 1–2)
Methods		
Participants	3	The 'reference' study population is described on pp. 3–4, including details of inclusion and exclusion criteria. The actual study population is described in the Results (see Participant flow, item 13)
Interventions	4	The interventions, i.e. MIDCAB and PTCA, are described on p. 6. References are cited to other descriptions of MIDCAB
Objectives	5	The objectives and hypotheses are set out on pp. 1–2
Outcomes	6	The outcomes are described on pp. 6–7 and 11–12, including an explicit statement of the primary outcome, i.e. the combined endpoint of survival free from death or cardiac-related events
Sample size	7	The target sample size, and the rationale for this target are described on pp. 3–4
Randomisation	8, 9, 10	Sequence generation, allocation concealment and implementation of randomisation are described on p. 5
Blinding	11	Details about blinding are reported on p. 7 and 11, including precautions against bias given that outcome assessment could not be blinded
Statistical methods	12	Details of the statistical methods used are described on pp. 8–9 and 12. No subgroup analyses were planned or carried out. For the primary outcome, both ITT and explanatory analyses were planned
Results		
Participant flow	13	A CONSORT flow chart for the trial is provided in *Figure 1*
Recruitment	14	Further details about recruitment are described on p. 13
Baseline data	15	Baseline data are presented in *Tables 6* and *7*
Numbers analysed	16	Numbers analysed for different outcomes are presented in *Tables 6–9* and *12–17*. The text on p. 19 states that all randomised patients were included in the ITT analysis of the primary outcome. A similar statement describes the numbers in the explanatory analysis of the primary outcome, p. 19
Outcomes and estimation	17	Outcomes are shown in *Tables 12–17* and *Figures 2* and *3*. Confidence intervals are reported for all estimates of effectiveness
Ancillary analyses	18	The secondary, explanatory analysis of the primary outcome measure was planned
Adverse events	19	Short-term adverse events and complications are described in *Table 8*, and longer-term cardiac-related events in *Table 11*
Comment		
Interpretation	20	Alternative explanations for the findings of the trial are described on p. 31
Generalisability	21	A statement is included on p. 29 describing our opinion on the applicability of the trial results
Overall evidence	22	The trial findings are placed in the context of other research, and a meta-analysis of published trials, including AMIST, is presented on pp. 29–30

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Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

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