INDICATIONS FOR PERCUTANEOUS AND SURGICAL REVASCULARISATION: HOW FAR DOES THE EVIDENCE BASE GUIDE US?

P M Schofield

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The treatment of patients with coronary artery disease continues to evolve, including those presenting with stable angina pectoris as well as those presenting with acute coronary syndromes. Pharmacological treatments which have changed practice in recent years include statins, angiotensin converting enzyme inhibitors, clopidogrel, and glycoprotein IIb/IIIa inhibitors. There have been major changes in percutaneous coronary intervention (PCI), particularly with the introduction of coronary artery stents. More recently, the appearance of drug eluting stents which may modulate smooth muscle cell proliferation has generated interest, as well as the use of adjunctive pharmacological treatment with stenting. In terms of surgical revascularisation, practice continues to evolve. There has been an expansion in the use of arterial conduits in order to improve long term graft patency. Less invasive approaches for surgery have been developed, as well as the use of "off-pump" coronary artery bypass graft surgery (CABG), in an attempt to reduce the risks associated with surgical revascularisation. Figure 1 shows the increase in the number of both percutaneous and surgical revascularisation procedures undertaken in the UK during the last decade.

With this background of continued development of revascularisation techniques together with the introduction of new technologies, it is clear that comparative trials of different approaches for revascularisation in certain clinical situations run the risk of being "out of date" before the study is completed and analysed. In addition, there are often several revascularisation options which could be applied to a particular clinical problem. We will attempt to outline the potential benefits of some of the newer approaches, as well as reviewing some of the comparative trials, which may be of use when managing individual patients who present with problems related to coronary artery disease.

CHANGES IN PERCUTANEOUS CORONARY INTERVENTION (PCI)

Percutaneous balloon angioplasty has been used to treat patients with coronary artery disease since the procedure was first reported by Gruntzig in 1979. Balloon inflation produces circumferential and longitudinal splits in the plaque, which because it contains tissue elements that make it elastic, retracts with a consequent reduction in stenotic area. The procedure can be complicated in the acute phase by spasm, thrombus formation or dissection of the vessel at the site of balloon dilatation. There is, therefore, a requirement for emergency coronary bypass surgery if the vessel occludes and causes acute ischaemia/infarction. The major limitation of balloon angioplasty has been the late occurrence of restenosis following the procedure. In the first few months following the procedure, the vessel undergoes a number of responses to the "damage" that is produced as part of the repair process. Growth factors are produced locally which result in new scar tissue forming inside the artery at the site of balloon injury, which reduces the luminal diameter. It has become clear, however, that restenosis is not only caused by tissue hyperplasia. Intravascular ultrasound studies have shown that vessel recoil and a process termed "negative remodelling" are also important contributory factors. Negative remodelling is the opposite process to that which normally occurs in atheromatous arteries. When an artery becomes progressively narrowed by atheromatous tissue it grows in size to "accommodate" the progressive narrowing. Following balloon angioplasty the artery actually gets smaller as the restenotic tissue forms—negative remodelling.

The ACME trial compared balloon angioplasty with medical treatment for patients with single vessel disease and exercise induce myocardial ischaemia.[1] Those who underwent intervention were more likely to be free of angina at six months than those treated medically, and were largely not taking anti-anginal medication. They also experienced a much greater increase in exercise duration. The value of balloon angioplasty in terms of symptomatic improvement was also demonstrated in the RITA 2 trial.[2]

In 1994 Mick and colleagues[3] published longer term observational outcome data for balloon angioplasty in 5000 patients followed for over five years. The in-hospital death rate was 0.5% and one and five year survival rates were 97.6% and 91%, respectively. Event-free survival at three years, however, was only 70% with most clinical events (reinvestigation and reintervention) occurring

Correspondence to:
Dr PM Schofield, Papworth Hospital, Papworth Everard, Cambridge CB3 8RE, UK;
peter.schofield@papworth-tr.anglox.nhs.uk

Developments in myocardial revascularisation

(1) Percutaneous coronary intervention (PCI)
- Coronary artery stenting
- Coronary brachytherapy
- Drug eluting stents

(2) Coronary artery bypass graft surgery (CABG)
- Increased use of arterial conduits
- Minimally invasive approach to surgery
- Off-pump CABG

within the first six months. Ten year follow up of the patients originally treated with balloon angioplasty in Zurich between 1977 and 1980 reported an overall survival of 89.5% (95% in those with single vessel disease and 81% in patients with multi-vessel disease). Angiographic restenosis was 31% at six months with very few patients developing restenosis between six months and 10 years. Of patients who had successfully dilated single vessel disease, 79% were free of angina at 10 years. It was considered that coronary artery stents, by increasing the size of the arterial lumen post-procedure and preventing early and late shrinkage, may allow better accommodation of any tissue growth so reducing symptom return and the need for a repeat procedure.

Coronary artery stenting has produced a beneficial effect on the outcome following PCI both in the acute phase as well as the longer term outcome. When extensive dissection occurs during balloon angioplasty resulting in vessel occlusion or threatened occlusion, coronary stenting restores flow by acting as a scaffold. Therefore, the use of stents has reduced the requirement for emergency CABG despite an increase in the complexity of disease and an increase in extent of disease being treated by PCI. In addition, the use of coronary stents has resulted in less angiographic and clinical recurrence following the procedure. Since a larger vessel lumen can be achieved and maintained with stenting, there is less impact of any restenotic tissue. The effects of elastic recoil and negative remodelling which may occur following balloon dilatation are essentially prevented by the use of coronary stenting.

The early trials of coronary stenting clearly demonstrated that in native vessels there was a reduction in the problem of restenosis.[4 5] In the Benestent study,[4] the primary clinical end points of myocardial infarction, need for coronary artery bypass grafting or repeat intervention and stroke has a relative risk of 0.68 (95% confidence interval 0.5 to 0.92) with stenting as compared to balloon angioplasty alone. The angiographic restenosis rate, measured quantitatively on follow up angiogram, was 22% for stenting and 32% for balloon angioplasty. In the STRESS trial[5] the angiographic restenosis rate was 29% for stenting and 42% for balloon angioplasty. Since these landmark trials there have been further studies published which demonstrate that almost any stent which produces a large lumen acutely will reduce the clinical restenosis rate to between 15–20% as compared with 35% for balloon angioplasty alone. Clearly, the clinical restenosis rate (that is, recurrent symptoms and angiographic restenosis) is always lower than the angiographic restenosis rate. With these trials there is some degree of patient selection and they may not necessarily reflect "real life" practice. It is likely that the restenotic rates are higher when stenting small vessels (< 2.5 mm in diameter) and when multiple stents are deployed.

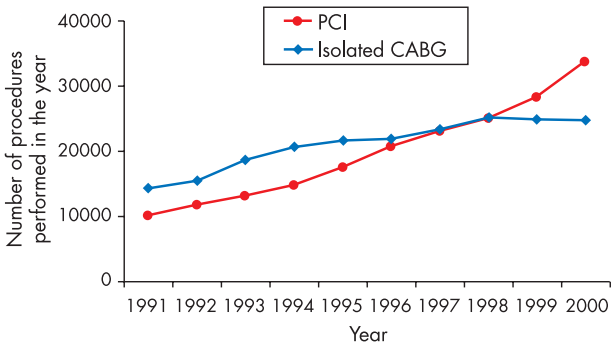

Figure 1 Number of procedures performed each year for coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) in the UK between 1991 and 2000.

Although the growing use of coronary stents has improved the results of percutaneous coronary revascularisation, the problem of in-stent restenosis continues to limit its long term success. More recently, radiation treatment (brachytherapy) has been used to treat patients with in-stent restenosis and recurrent restenosis has been reduced using β radiation and γ radiation.[6] Brachytherapy is at the moment the most effective technique for treating the problem of in-stent restenosis.

Several pharmacological agents have been used over the years to reduce the incidence of restenosis following PCI. None has been shown to be effective. In contrast, the systemic and local delivery of sirolimus (rapamycin), which inhibits cytokine mediated and growth factor mediated proliferation of lymphocytes and smooth muscle cells, has been shown to be effective. A recent trial comparing a standard stent with a sirolimus eluting stent has generated much interest (RAVEL study).[7] The primary end point was in-stent late luminal loss—the difference between the minimal luminal diameter immediately after the procedure and the diameter at six months. This was significantly lower in the sirolimus stent group (mean (SD) −0.01 (0.33) mm) than in the standard stent group (0.80 (0.53) mm). None of the patients in the sirolimus stent group had restenosis of 50% or more of the luminal diameter, as compared with 26.6% of those in the standard stent group. During a follow up period of up to 12 months, the overall rate of major cardiac events was 5.8% in the sirolimus stent group and 28.8% in the standard stent group. The difference was due entirely to a higher rate of revascularisation of the target vessel in the standard stent group. Even though only relatively uncomplicated lesions were studied, the results of the RAVEL study were striking, since the drug eluting stent virtually eliminated angiographic evidence of neointimal hyperplasia and restenosis and greatly reduced the need for repeated revascularisation procedures. Similar studies of stents coated with the antineoplastic agent paclitaxel, which like sirolimus inhibits cell division, are in progress and the preliminary results are most encouraging. It is likely that the introduction of drug eluting stents will be a major advance in PCI with the advantage of reducing its greatest drawback—re-stenosis (fig 2).

CHANGES IN CORONARY ARTERY BYPASS GRAFT SURGERY (CABG)

Favoloro first described the use of saphenous vein to bypass a diseased coronary artery in 1968.[8] Since that time CABG has become the most common operation for ischaemic heart disease and one of the most commonly performed surgical

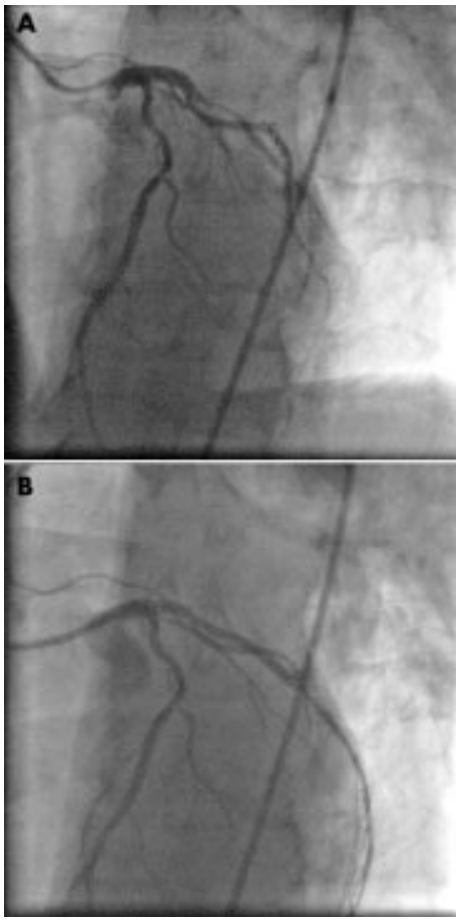

Figure 2 Left coronary angiogram showing a proximal stenosis in the circumflex artery (A) before and (B) after the deployment of a drug eluting stent. Left anterior oblique projection.

operations worldwide. It is also the most studied, documented, evaluated, and audited treatment in the history of medicine. There are two broad indications for CABG: symptomatic and prognostic. The former involves patients whose angina is not adequately controlled by medical treatment. The latter indication is the presence of coronary artery disease which has been shown to probably have a better prognosis with surgery than with medical treatment. Such disease, in descending order of prognostic importance, includes: (1) significant (more than 50%) stenosis of the left main stem; (2) significant proximal stenosis of the three major coronary arteries; and (3) significant stenosis of two major coronary arteries, including high grade stenosis of the proximal left anterior descending artery. The presence of impaired left ventricular function increases the prognostic advantage of surgery over medical treatment in all categories. Much of this information is obtained from an extensive list of publications derived from two major randomised studies of coronary surgery: the American CASS study[9] and the European coronary surgery study.[10] Early reports of these studies showed the symptomatic advantage of CABG over medical treatment. As follow up lengthened with time, the prognostic advantages began to emerge in a number of categories.

The operative mortality for CABG in the absence of any risk factors is less than 0.5%. Risk factors which contribute to higher mortality after CABG are age, female sex, impaired left ventricular function, severe pulmonary, neurological and renal dysfunction, extracardiac arteriopathy, and emergency or repeat operation. The overall operative mortality for CABG is between 2–4%. There are elaborate risk stratification methods available for the assessment of risk in individual patients, which can be further adjusted for particular surgeons or institutions. There is the paradox that the higher the risk of operation, the greater is the benefit of surgical over medical treatment.

Trial acronyms

ACME: Angioplasty Compared with Medicine
ARTS: Arterial Revascularisation Therapies Study
BARI: Bypass Angioplasty Revascularisation Investigation
CABRI: Coronary Angioplasty versus Bypass Revascularisation Investigation
CASS: Coronary Artery Surgery Study
EAST: Emory Angioplasty Surgery Trial
RAVEL: Randomized study with sirolimus coated BX Velocity balloon Expandable stent in the treatment of patients with de novo native coronary Lesions
RITA: Randomised Intervention Treatment of Angina
STRESS: Stent Restenosis Study

Most patients are angina-free following CABG, but recurrent angina may occur in the years after surgery. The development of angina post-CABG may be caused by progression of disease in the native vessels, so that new stenoses appear in previously healthy ungrafted vessels, or in grafted vessels beyond the site of graft anastomosis. Although the long term patency rates for the left internal mammary artery graft are extremely good, saphenous vein grafts have a significant rate of attrition. Thrombotic occlusion can occur in the early postoperative period and later on the vein can develop graft disease. This is caused by intimal hyperplasia with smooth muscle proliferation leading to stenosis and finally occlusion. The patency rate of vein grafts is around 50% at 10 years.

In patients with three vessel coronary artery disease, the standard procedure has been to graft the left anterior descending artery with the left internal mammary artery and use the saphenous vein for the other bypass grafts. Since at least 70% of patients are alive 10 years following surgery, the recurrence of symptoms from vein graft disease remains a clinical problem. In recent years, the increasing use of arterial conduits has changed the nature of the standard CABG. Large observational studies have shown that the use of the left internal mammary artery graft improves survival and reduces the incidence of late myocardial infarction, recurrent angina, and the need for further cardiac interventions.[11] The possibility that bilateral internal mammary artery grafts offer additional clinical and survival benefits as compared with a single internal mammary artery graft has been addressed in observational studies. Recent publications have suggested benefit for bilateral mammary grafting, including a large series from the Cleveland Clinic.[12] There seemed to be significant survival benefit when using bilateral mammary artery grafts irrespective of age, ventricular function, and presence of diabetes. In addition the benefit of using bilateral mammary grafting increased with the duration of follow up, particularly in terms of the need for redo surgery, which at 10 years was 40% for single mammary grafting and 8% for bilateral grafting in matched patients. At 10 years post-CABG over 90% of internal mammary artery grafts continue to function well. In terms of morbidity for bilateral mammary artery grafting, sternal dehiscence as a consequence of sternal devascularisation is the most worrying complication, particularly in diabetics. The

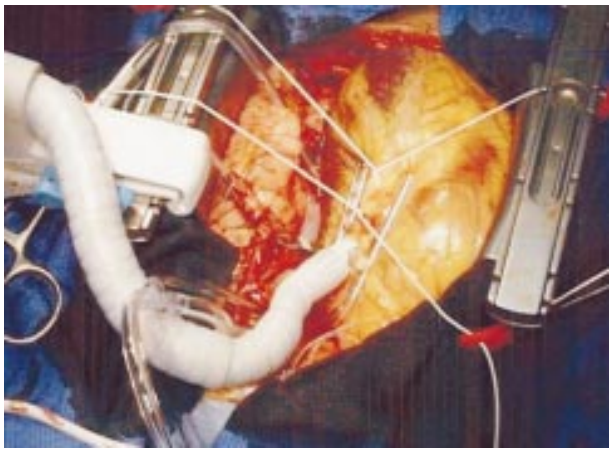

Figure 3 "Off-pump" coronary artery bypass surgery. The stabiliser is in position.

risk is two to three times that of single mammary artery grafting. Other arterial grafts which have been utilised include the radial artery and the gastroepiploic artery. Again, angiographic follow up has confirmed patency rates of greater than 90% in the first few years following surgery. There has therefore been a move in recent years towards more arterial revascularisation and away from saphenous vein grafts in an attempt to reduce the requirement for further intervention in the years following coronary surgery.

Although CABG using cardiopulmonary bypass (extracorporeal circulation and pump oxygenator) remains an effective treatment for patients with coronary artery disease, it is associated with some morbidity as well as mortality. Cardiopulmonary bypass requires full heparinisation, induces a whole body inflammatory response, and generates microemboli. It also requires cannulation and cross clamping of the ascending aorta, which may lead to atheromatous macroemboli. Procedures which do not utilise cardiopulmonary bypass may reduce these unwanted effects. It has been suggested that "off-pump" CABG, which avoids cardiopulmonary bypass, will lead to a reduction in perioperative morbidity and mortality. Recently cardiac stabilisation techniques have been developed to facilitate surgery on the beating heart during off-pump CABG and even patients with three vessel disease can be treated in this way (fig 3). Randomised trials comparing off-pump CABG with standard CABG have now been published.[13 14] Although blood products were needed less during off-pump CABG as compared with standard CABG (3% *v* 13%) and the release of creatine kinase muscle-brain (CK-MB) isoenzyme was 41% less in the off-pump group, there were no differences in perioperative complication rates. At one month, there was no difference in the proportion of patients surviving free of cardiovascular events.[13] In a UK study, in-hospital morbidity was lower in patients who had off-pump CABG than in those who had standard CABG. This included perioperative atrial fibrillation, chest infection, and blood transfusion. There was no difference in outcome in the first 1–3 years after surgery between the two groups.[14] This is an important issue, since it is vital that the quality of the anastomosis is as good with the beating heart technique as it is with the heart arrested.

There has also been an interest in "minimally invasive direct coronary artery bypass" (MIDCAB) procedures in an attempt to reduce the morbidity and mortality following CABG. The technique aims to avoid a full sternotomy, cardiopulmonary bypass, and aortic manipulation. Thereby, it is hoped that it will reduce morbidity, length of stay, and cost associated with surgery. Using a thoracic MIDCAB approach, it is possible to access all three major coronary arteries. With an extrathoracic MIDCAB approach it is possible to achieve multi-vessel arterial grafting. Minimally invasive coronary bypass surgery remains under clinical investigation. Hybrid procedures have also been developed, with left internal mammary grafting to the left anterior descending artery using MIDCAB and coronary stenting of lesions in the circumflex and/or right coronary arteries.

Table 1 Comparative trials of percutaneous coronary intervention and coronary artery bypass graft surgery

		Number of patients randomised
BARI[15]	PTCA *v* CABG	1829
CABRI[16]	PTCA *v* CABG	1054
EAST[17]	PTCA *v* CABG	392
RITA[18]	PTCA *v* CABG	1011
ARTS[20]	Coronary artery stenting *v* CABG	1205

CABG, coronary artery bypass graft surgery; PTCA, percutaneous transluminal (balloon) coronary angioplasty.

COMPARATIVE TRIALS OF PCI AND CABG

There have been randomised prospective trials comparing PCI with CABG, mainly in the "pre-stent" era (table 1). The BARI study involved over 1800 patients with multi-vessel disease but no previous myocardial revascularisation.[15] There was no difference in in-hospital mortality or five year mortality between the two groups. Within five years of randomisation 8% of CABG patients and 54% of angioplasty patients required an additional revascularisation procedure. However, 69% of angioplasty patients avoided CABG during this period and 45% required only one angioplasty procedure. Both treatment strategies relieved angina but anti-anginal drug use was lower in the CABG patients. The CABRI study randomised patients with angina or inducible ischaemia and stenoses in two or more major epicardial arteries.[16] Patients with significant left main stem disease or ejection fractions below 35% were excluded. Again, there was no difference in mortality between the two groups, but a significantly higher rate of repeat revascularisation in the angioplasty group. The EAST trial randomised patients with multi-vessel disease, but excluded patients with left main stem disease, myocardial infarction within the previous five days, and those with ejection fractions below 25%.[17] The combined main trial end point of death, non-fatal myocardial infarction or a large ischaemic defect on a stress thallium scan occurred in 27.3% of the surgical group and 28.8% of the angioplasty group, the difference clearly not being significant. There was an increased requirement for repeat revascularisation procedures in the angioplasty group. The RITA trial randomised patients to CABG or angioplasty with stratification into groups with one, two or three vessels requiring treatment.[18] Patients with left main stem disease were excluded, and of those randomised 45% had single vessel disease. The primary end point was death or myocardial infarction and there was no significant difference between the two groups at five year follow up. Repeat coronary angiography was four times more frequent in the angioplasty group and there was a higher incidence of angina in the angioplasty group at six month follow up. At two year follow up the angina

Indications for percutaneous and surgical revascularisation: key points

- The techniques used for both percutaneous and surgical revascularisation continue to evolve
- Most patients with significant left main stem disease are currently treated by coronary artery bypass grafting (CABG)
- Patients with single or multi-vessel disease are likely to be treated by percutaneous coronary intervention (PCI) if their disease is suitable for this approach
- Drug eluting stents are likely to have a major impact on coronary intervention
- It is probable that more "off-pump" CABG will be performed in the future

rate for angioplasty patients had not changed (31% *v* 32% at six months) but had risen in the surgical group (22% *v* 11%).

Published meta-analysis of these various trials[19] indicate that the results are remarkably similar and that there is no major difference in mortality between the two treatments at one and three years. Further intervention is required more frequently in the angioplasty patients—in the first year 33.7% of patients initially treated with angioplasty required a further procedure compared to 3.3% of those treated with surgery. Since problems with angioplasty restenosis occur in the first six months but over a longer period for those treated with CABG, it is not surprising that the difference is less striking over subsequent years. While angina rates were higher at one year after angioplasty, by three years the incidence of angina was the same in both groups. It has been proposed that longer term follow up will favour angioplasty over CABG in view of the progressive graft attrition rate following surgery.

Since these trials were carried out, improvements in percutaneous and surgical techniques may now limit the validity of any conclusions that have been drawn from the earlier studies. Re-evaluation may be particularly important in the case of PCI, since studies have shown that stenting necessitates fewer repeat revascularisation procedures than angioplasty alone. In the ARTS study patients were randomised to coronary stenting or CABG when an interventional cardiologist and cardiac surgeon agreed that the same extent of revascularisation could be achieved by either technique.[20] The primary clinical end point was freedom from major adverse cardiac and cerebrovascular events at one year (that is, freedom from a composite of death, myocardial infarction, cerebrovascular event, and further revascularisation). Over 1200 patients were randomised; patients with occlusion of more than one major epicardial vessel, myocardial infarction within the preceding week, a left ventricular ejection fraction of less than 30%, or severe renal or hepatic dysfunction were excluded. At one year there was no significant difference between the two groups in terms of the rates of the composite of death/myocardial infarction/cerebrovascular event, which were 9.4% for PCI and 8.7% for CABG. The need for additional revascularisation was 16.8% in the stented group and 3.5% in the CABG group. This level of repeat revascularisation in the stented group was noted to be less than that found in the pre-stent era and was attributed to a reduction in the rate of restenosis. The rate of event-free survival at one year was 73.8% in the stented patients and 87.8% in those undergoing CABG. The costs of the initial procedure were less for patients assigned to stenting than for those assigned to CABG, but this difference was reduced during follow up because of the increased need for repeat revascularisation. After one year, however, there remains a substantial difference in costs, in favour of PCI. In a pre-specified subanalysis of the ARTS trial, the outcomes in patients with stable angina were compared to those with unstable angina. There was no difference in the rates of death, myocardial infarction, and cerebrovascular event at one year in patients with unstable angina treated with either coronary stenting or CABG compared with patients with stable angina. The rate of repeat revascularisation of both unstable and stable angina patients was significantly higher in patients with stents.

CONCLUSION

The published trials of PCI and CABG do help to guide the management of patients with coronary artery disease. In recent years, there has been a progressive increase in the number of patients undergoing revascularisation, particularly using a percutaneous approach. Since practice evolves continuously, it is likely that the treatment strategies will have changed by the time a large randomised trial reaches publication. For example, since the ARTS trial was initiated in 1997 (with publication in 2001), surgical practice has changed with more patients undergoing off-pump CABG and more widespread use of minimally invasive approaches. Similarly, more patients undergoing PCI are now receiving adjunctive treatment with glycoprotein IIb/IIIa inhibitors. It is also likely that the introduction of drug eluting stents will have a major impact on practice.

At the present time, it is probable that most patients with significant left main stem disease will be treated by CABG, whereas those with single vessel coronary artery disease will be treated by PCI. In patients with multi-vessel disease who are suitable for treatment using either PCI or CABG, the patient and physician have a dilemma. Both approaches have a similar combined rate of death, myocardial infarction or cerebrovascular event. CABG carries a lower rate of repeat revascularisation in the first 12 months, whereas PCI is less invasive and less expensive. Clearly, the views of the patient are particularly important in choosing an approach. Although both CABG and PCI continue to develop, as time goes by it seems as though the scales are tipping towards a percutaneous approach in patients with multi-vessel disease which is suitable for this treatment option.

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