CORONARY ARTERY STENTS

Authors: Catherine Meads, Carole Cummins
and Andrew Stevens

Department of Public Health & Epidemiology
University of Birmingham
Edgbaston
Birmingham
B15 2TT

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Contents

1. Summary

- Coronary artery disease is a major cause of morbidity and mortality in the UK and is a major cost to the health services. The clinical effects of coronary artery disease include angina and acute myocardial infarction. Treatment for coronary artery disease includes drug therapy, attention to risk factors, invasive therapy including with percutaneous transluminal coronary angioplasty (PTCA) and stents and coronary artery bypass graft (CABG) surgery.

- This report examines the costs and benefits of routine stenting (i.e. not in an emergency) compared to PTCA alone, medical treatment and coronary artery bypass grafting (CABG) for native coronary artery disease (i.e. not in a graft vessel).

- Medline, BIDS ISI and Embase databases were searched for randomised controlled trials (RCT) of coronary artery stent use. A separate search was carried out for economic evaluations of stents.

- Eleven RCTs were found which compared stents to PTCA in a variety of subgroups of patients. None were found comparing stents to medical treatment or CABG. For the eleven RCTs the clinical outcome measures of incidence of death, myocardial infarction (MI), repeat revascularisation (CABG or repeat PTCA), event free survival and angina free survival are reported. Follow up on all eleven RCTs was for one year or less. Meta analyses showed that there was a reduced risk of the need for repeat PTCA and target vessel revascularisation in the stent group compared to the PTCA group but no evidence that stents reduce the risk of death, MI or need for CABG. For the stent group there was also a small increased chance of being angina free at the end of the trials and event free survival (no adverse event occurring during the one year follow up period).

- Four cost effectiveness studies were found based on three of the eleven RCTs and two cost utility studies, one based on the BENESTENT trial. Only the BENESTENT-II trial included costs and cost effectiveness as part of the trial design. The cost utility studies estimated additional costs per quality adjusted life year (QALY) gained at US$23,600 (£14,750) and £250,000.

- The BENESTENT-II trial effectiveness results were used as the basis for a new cost utility analysis. The costs used were derived from a local Birmingham NHS trust's published tariffs for treatment. The benefit calculation showed the increase in quality adjusted life years (QALYs) from PTCA to stent to be very small (0.04 QALYs per person). The cost utility analysis derived an additional cost per QALY if a single stent is used instead of PTCA of £22,975 and if two stents are used of £41,500. Sensitivity analysis around the assumptions made gave an incremental cost per QALY gained of single stent over PTCA of between £13,000 and £53,000.

2. Introduction

Coronary artery disease is a major cause of morbidity and mortality in the UK. The effects of coronary artery disease include angina and acute myocardial infarction. Treatment for coronary artery disease includes drug therapy, attention to risk factors, invasive therapy and/or surgery. The cost of coronary artery disease is considerable, impinging on primary health care, hospital inpatient and outpatient facilities and emergency services.

Coronary artery stents are, in essence, short prosthetic linings for coronary arteries. They are a relatively new technology, used as an adjunct to percutaneous transluminal coronary angioplasty (PTCA). These treatments are used in the invasive management of coronary artery disease. This report examines the costs and benefits of using stents compared to PTCA and compared to medical treatment and coronary artery bypass grafting (CABG) for native coronary artery disease.

3. Background

3.1 Natural history

Coronary artery disease (ischaemic heart disease) is a disorder of the cardiovascular system where the coronary arteries supplying the heart muscle become partially or completely blocked. The clinical presentation of coronary artery disease can be stable or unstable angina, myocardial infarction or sudden death. In some cases, coronary artery disease can be silent until complications appear. The vast majority of coronary artery disease is due to atheroma and its complications. Patches of damage to the linings of blood vessels, mostly in the proximal coronary arteries, lead to the formation of atheromatous plaques - raised patches of fibrous and fatty material. These plaques cause narrowing or blockage of the lumen which causes lack of oxygenated blood to the heart muscle, resulting in the symptoms of stable angina. Partial obstruction may be made worse by spasm of the arterial walls. Significant reduction of blood flow does not occur until the lumen is narrowed to less than 50%. Unstable angina (recurrent attacks of angina at rest or increasing frequency or severity of angina on exertion) is usually attributed to rupture of an atheromatous plaque in a coronary artery. The associated blood clot causes severe narrowing of the vessel. Sudden complete obstruction of a major artery is usually due to a similar process and results in myocardial infarction (MI), where the lack of blood borne oxygen leads to heart muscle cell death.

The impact of angina on a patient's quality of life can range from very mild pain on exertion to severe, disabling pain at rest. Stable angina of effort has been classified into four grades by the Canadian Cardiovascular Society.[1] Unstable angina has been classified into three grades of severity and clinical circumstances by Braunwald [2] (see Appendix 1).

Investigation of coronary artery obstruction includes coronary angiography where a catheter is inserted into the coronary arterial tree and X-ray contrast media injected. This indicates the position and severity of the coronary disease and is essential whenever CABG or PTCA is being considered.

The goals of treatment of coronary artery disease are to

- prolong life,
- prevent myocardial infarction,
- to relieve angina and other symptoms
- to improve quality of life
- to prevent heart failure

These are achieved either by maintaining or improving coronary artery blood supply or by reducing the oxygen requirements of the heart muscle.

3.2 Incidence/prevalence

The number of people for whom stents might be used if shown effective can be estimated from the following:

As with many diseases, there are no national data on the incidence rates of coronary artery disease as a whole.[3] The Welsh Heart Survey and the British Regional Heart Study estimated that 25% of middle aged men show some evidence of heart disease.[3] It is also estimated that the prevalence of coronary artery disease in women (before the menopause) is approximately half that found in men.[3] Coronary artery disease is the major cause of death of men and women in the UK,[4] causing approximately 25% of all deaths in 1994. These were mainly recorded as acute myocardial infarction and chronic ischaemic heart disease.

The Fourth General Practice Morbidity Survey (1991-1992)[5] gives the prevalence and incidence rates per 10,000 person years at risk for acute myocardial infarction and angina pectoris[6.] (see Table 1). Comparison of the Fourth to the Third General Practice Morbidity Survey (1981) suggests that the rates for angina are rising.[5]

Table 1: Incidence and prevalence rates of acute myocardial infarction (AMI) and angina per 10,000 person-years at risk.

prevalence	Males	females	incidence	males	females
AMI	38	20		29	16
angina	130	98		55	49

3.3 Service Provision

In the West Midlands, with a population of 5,254,900, there will be approximately 23,500 new consultations for myocardial infarction and 54,500 new consultations for angina in one year.

For most of these patients, the appropriate treatment remains with the GP. Only a small proportion are referred to hospital cardiology departments. These tend to be patients with more severe angina, which is not controlled by anti-anginal medications[7] and those at highest risk of repeat MI.

In 1992 76,296 coronary angiograms, (1,325 per million population) were performed in the UK as a whole. 11,575 PTCAs were performed in the same year.[8] The rates of PTCAs performed in the UK are gradually increasing.[9] In the West Midlands, the number of PTCAs rose from 607 in 1993/4 to 1,155 in 1995/6.[10] During the same time period the number of CABGs increased from 1,820 to 2,017.[10]

The use of coronary stents in Europe has been steadily increasing from about 2,000 in 1991 to nearly 8,000 in 1993.[11] In 1995 stents were used in the vast majority of coronary angioplasty procedures at some leading centres and with a frequency of 25-50% at other centres.[12] Exact details of current practice are difficult to assess because the evidence indicates that current usage of stents is changing very rapidly. Figures for Greater Glasgow health authority show that in 1994/95 10% of PTCA had a stent inserted. By 1996/7, this had risen to 20%.[13]

Anecdotal evidence suggests the use of stents in up to 70% of patients having PTCA in one consultant's practice in the West Midlands.[14]

3.4 Current treatment alternatives

3.4.1 Medical management

Medical management is the initial treatment of choice. Anti-anginal drugs include nitrates, beta blockers and calcium antagonists. Drugs for the prevention of blood clots include aspirin, ticlopidine, heparin and warfarin. Dipyridamole is now no longer used. (Abciximab has started to be used with the aim of increasing the effectiveness of PTCA.) Blood clot dissolving drugs used in unstable angina and following MI include streptokinase and tissue plasminogen activator. Medical management of coronary artery disease also involves attention to risk factors eg. with cholesterol lowering drugs and anti-hypertensive treatment[1] and by encouraging exercise.

In some patients with stable angina, medical management fails to control symptoms. In these patients and patients with unstable angina and following MI, invasive treatment is considered. It is also considered occasionally for patients with a strongly positive exercise test of myocardial ischaemia where medical treatment does control symptoms.

- Before stents were available, patients with coronary artery disease not responding to medical treatment received either CABG or PTCA. CABG is a major operation whereas PTCA is simpler and does not require a general anaesthetic.

One patient may undergo one or several treatments during one episode of coronary artery disease.

3.4.2 Coronary artery bypass graft

CABG was pioneered in 1967[9] and has been used increasingly since then.

CABG is a surgical technique which involves opening the chest wall, where a blocked or narrowed section of a coronary artery is bypassed using part of a vein or artery taken from elsewhere in the patient's body.

CABG can be a planned or emergency procedure and is carried out by cardiothoracic surgeons. It is usually used for the more severe cases of coronary artery disease. Indications include unstable angina, severe stable angina not responding to medical

treatment, marked changes in exercise ECG, left main stem stenosis and severe triple vessel disease. It can be used in patients with chronic stable angina, unstable angina, following myocardial infarction or following complications from PTCA.

The advantages of CABG include complete relief from angina in 60-90% of patients at one year, a slight decrease in mortality when compared to medical treatment[9,15,16] and lower revascularisation rates after 1 year when compared to PTCA.[15,17]

The disadvantages to CABG are the cost and morbidity of the operation , a slightly higher rate of MI when compared to medical treatment [15] and the time spent in hospital and for convalescence.[15] Mean length of stay post-operatively in uncomplicated cases is 7-10 days.[9] Following hospital discharge, recovery takes longer after CABG when compared to PTCA.[15,16,18] Some patients are insufficiently fit for a major operation. In the longer term, progression of coronary artery disease often occurs in native or graft vessels.

3.4.3 Percutaneous transluminal coronary angioplasty

PTCA was first used in 1977 and first described by Gruentzig in 1978.[19]

PTCA is a technique in which the narrowed or blocked parts of coronary arteries are dilated by passing a radiographically guided catheter with a small balloon, usually from the femoral artery, into the narrowed section of the coronary artery and then inflating it to high pressure for a short time. The balloon is then deflated and withdrawn, leaving the coronary artery with a wider lumen than before the procedure[9] but with a very disrupted surface.[20]

PTCA provides an invasive treatment available to the physician that increases the blood supply to the heart muscle. PTCA is usually used in less severe forms of coronary artery disease such as single or double vessel disease.[21] It is considered when medical treatment has failed to control symptoms. Indications for PTCA have been listed to include chronic stable angina, unstable angina, following myocardial infarction, patients with stenosed CABG grafts, patients in whom CABG is deemed inappropriate, cardiogenic shock, asymptomatic patients and repeat PTCA for return of symptoms.[9]

PTCA does not require a general anaesthetic or necessitate opening the chest wall so it is also useful in those who are poor operative risks.[9] Length of stay in hospital is short (mean in 1994 was 4.32 days[22] and is gradually decreasing), can be carried out as a day case[22] and there is no need for prolonged convalescence.[9]

There are two main problems with PTCA. One is that, during the procedure the artery may close abruptly, leading to a myocardial infarction or, in rare cases, death. Abrupt closure during PTCA still occurs in 2-10% of patients[23] and this has required emergency CABG back-up to be available.[20,21] The second main complication is that between 15-52% of target arteries may narrow again after a few months following an initial successful PTCA.[24] These patients will then require further treatment which could be CABG, PTCA or medical treatment.

Various transluminal techniques have been developed to enhance the results of PTCA. These include stents which widen the arterial lumen and lasers and rotablators which remove atheromatous plaques from arterial walls.

3.4.4 Appropriate use of treatments

There exists a large descriptive and analytical literature on the characteristics and outcomes of patients undergoing invasive cardiac procedures. Various guidelines on CABG and PTCA have been produced by the British Cardiac Society[20] and by the American College of Cardiology and American Heart Association(ACC/AHA).[9]

When compared to medical therapy, studies have shown that PTCA is probably more successful in treating angina, but at the cost of higher subsequent rates for MI and need for CABG.[7,25,26] Compared to CABG, PTCA is cheaper, involves a shorter hospital stay and is less painful to the patient.[15] Evidence suggests that more patients have angina 1 year after PTCA compared to CABG but the difference is not so marked after 3 years.[17] Mortality and MI rates are similar for both treatments but the reintervention rates are greater for PTCA.[17]

3.5 Outline of service to be evaluated

The service to be evaluated is for routine stent insertion during the PTCA procedure.

Stents are the most frequently used of the new additions to PTCA. They are intended to alleviate the two main disadvantages of PTCA, acute occlusion and long term restenosis, in as many lesions and patient subgroups as possible in a safe and cost effective manner.

Stents are a new technology and their design and use has been rapidly and continually evolving since their use was first reported in patients by Sigwart in 1987.[27] They are made from stainless steel, nitinol, or tantalum wire bent in a variety of ways to make coils or slotted tubes. Stents can have radioopaque end markers or can be coated with heparin.[27,28] There are currently approximately 50 different stents on the market.

Stents are inserted into coronary arteries and expanded onto the artery wall by using a PTCA balloon or a balloon catheter or in one case by retraction of a sheath. They provide a permanent 'scaffold' for the artery. In acute blockage of an artery, stents are intended to tack back flaps of the arterial wall caused by rupture of a plaque. This is known as 'bail-out' stenting and is intended to reduce the number of patients who need emergency CABG.[21] Stenting can, in theory, prevent gradual closure of the artery in long term restenosis by increasing the lumen diameter after the procedure and mechanically enforcing the vessel wall.[29]

Stents are 'foreign bodies' permanently implanted into arterial walls so there is a risk of blood clots forming and blocking the coronary artery or moving into the bloodstream to block arteries elsewhere in the body. Anticoagulation is used to prevent these potentially fatal complications.

There are several scenarios where the use of stents has been described.[27, 30]

1. Routine stenting to prevent and alleviate long term restenosis. If stents were not available treatment for long term restenosis would be by PTCA or elective CABG depending on severity of disease.
2. Routine stenting to prevent long term restenosis and potential acute arterial closure where there is doubt about the success of the PTCA (sub-optimal result). If stents were not available the treatment would be CABG if the artery closed following PTCA or no further treatment if the artery remained open following PTCA.
3. Rescue (bailout) stenting to alleviate acute closure provoked by an unsuccessful PTCA. If bailout stenting was not available then emergency CABG would be carried out.

4. Stenting in high-risk cases (ostial, bifurcation or diffuse lesions, chronic total occlusions, bypass graft lesions, in an artery that is the sole or major remaining source of blood to the heart muscle[30] and after MI). In this scenario stents have been considered as an alternative to elective CABG.

Stents are regularly used in the treatment for all the above scenarios.[31,32,33,34] A survey in Canada in 1996[35] showed the proportions of patients in whom stents were used in each scenario as follows: 1 - 36%, 2 - 30%, 3 - 5%, 4 - 27% (following MI - 2%).

This report examines the benefits and costs of routine stenting to prevent and alleviate long term restenosis in both low and high risk scenarios (i.e.1,2 and 4 above).

Potential Advantages Compared to PTCA Alone

For prevention of restenosis after a successful PTCA, the stenting procedure currently takes very little longer than PTCA on its own. Use of a stent may reduce the need for subsequent repeat intervention. More than one stent may be fitted during one procedure depending on the length of the lesion and whether there are multiple lesions suitable for stenting in different coronary arteries. (The time taken to insert the stent successfully depends partly on the operator's ability and experience and partly on the anatomy of the lesion to be stented.)

Potential Advantages Compared to CABG

The stay in hospital for elective stent procedures is for up to 3 days only, with some suitable patients being treated as day cases.[22] Some patients are insufficiently fit to undergo a major operation such as CABG. Bailout stenting, if it is successful, can be carried out at the same time as the PTCA by the same medical team and alleviates the need to undergo emergency CABG. The stay in hospital would be reduced, resulting in decreased medical costs and less trauma for the patient.

Anticoagulation

For the first few years that stents were being used, patients were given aspirin, dipyridamole, dextran, heparin, warfarin and calcium antagonists or a similar combination. This resulted in longer hospital stays and increased bleeding complications for stent patients compared to those receiving PTCA only. Antiplatelet therapy using Aspirin and Ticlopidine is now widely used, resulting in decreased bleeding complications and hence shorter hospital stays.[21,36,37,38] For a more complete review of the differences that changes in anticoagulant and antiplatelet therapy have made, see the CCOHTA report.[39]

Abciximab, a monoclonal antibody that inhibits platelet glycoprotein receptors, has recently become available. Although treatment with this drug is very expensive a recent randomised controlled trial found a lower rate of death, myocardial infarction or urgent revascularisation in stent with abciximab than in stent with placebo (5.3% compared with 10.8%, hazard ratio 0.48 (95% CIs 0.33-0.69).[40] Six month outcomes were reported in the EPILOG trial,[41] where there was no difference in the pre-specified endpoint between Abciximab and low dose heparin and placebo, although there was a difference between Abciximab and standard dose heparin and placebo. Attenuation of the 30 day risk difference largely resulted from the lack of any impact of Abciximab on non-urgent revascularisation. The CAPTURE trial also found no difference in deaths and myocardial infarction at 6 months.[42] Results in favour of Abciximab at 30 days have been reported for stent subgroups in the CAPTURE and EPILOG trials,[43] but the use of stents was discouraged in these trials, so patients are unlikely to be representative. The long term impact of Abciximab therapy in conjunction with stents is therefore unclear.

Uncertainties about treatment

The critical question in this report is whether stents are proven to confer any advantages over PTCA alone.

In addition it is uncertain as to whether single or multiple stents have the same effect.[27] Stents are made from differing materials, have different configurations, shapes and lengths. Some of the stents currently in use are not the same versions as those used in recent randomised controlled trials. Stents may work differently depending on which coronary artery is treated, the diameter of the vessel and whether it is a native coronary artery or saphenous vein graft.[27] From a mechanical point of view, flow and turbulence through different arteries will vary. Stent placement may or may not be similarly effective for de novo, restenotic or multiply restenotic lesions. Stents can not be removed from the coronary artery.[44]

4. Question addressed by this review

This report examines the costs and benefits of using stents following percutaneous transluminal coronary angioplasty (PTCA) compared to using PTCA alone and compared to medical treatment and coronary artery bypass grafting (CABG) in the invasive treatment of native coronary artery disease.

5. Methods

5.1 Search strategy

Medline (1993-August 1998) using the NHS Centre for Reviews and Dissemination search strategy for randomised controlled trials and the search terms 'stent$' and 'coronary'.
BIDS ISI (to August 1998) using search terms 'stent*+coronary+trial*'.
Embase on CD ROM (1991-1993, 1994-1995, 1996-Mar1997) using search terms 'stent', 'coronary artery' and 'clinical trial'.
Cochrane Library 1998 Issue 3.
References from relevant articles and conference proceedings abstracts were hand searched.
Reviews were obtained by personal contact with other clinical review specialists.
Unpublished trials were not sought.

The inclusion criteria for this study were any randomised controlled trials of stents vs. PTCA in the treatment of native coronary artery disease which have been fully reported in peer reviewed journals and not solely in the form of conference abstracts. (see Appendix 4)

5.2 Data extraction strategy

Data extraction was carried out by CM and CC and differences were discussed and resolved

The angiographic outcome measures extracted included reference diameter, minimal lumen diameter, % stenosis and rate of restenosis >50%. The clinical outcome measures included death, CVA, MI, reintervention with CABG and PTCA, angina free survival, event free survival (patient not suffering any adverse outcome) and change in angina grade.

5.3 Quality assessment strategy

The following factors were considered when evaluating the randomised controlled trials reviewed.

- Within each trial, whether the baseline characteristics and severity of disease were similar in the control and treatment groups
- The method of randomisation used, whether this was specified in the report and some indication of whether it was likely that clinicians had any knowledge of the treatment to be allocated to the next patient.
- The timing of outcomes, whether the specified timing was adhered to and whether the outcomes specified in the methods sections were reported in the results sections.
- Whether the drop-out rates and treatment failure rates for control and treatment groups were similar and if large, were explained in the text.
- The nature and extent of loss to follow up.
- Whether the analysis was carried out on an intention to treat basis.
- Whether the conclusions match the results.

5.4 Economic analysis methods

A separate search was carried out for economic evaluations of stents. Databases searched were Medline and the Cochrane library. References from relevant articles and conference proceedings abstracts were hand searched.

6. Quality, direction and strength of the evidence

6.1 Number and type of studies

Eleven randomised controlled trials were found that compared stents to PTCA in;

1. patients with stable angina and a single new coronary artery lesion (BENESTENT trial) [24,45,46,47,75]
2. patients with stable and unstable angina and a single new lesion (BENESTENT-II and STRESS trials) [28,48,49,50,51,52,53]
3. with a single new lesion of the right coronary artery only ("Switzerland" trial) [54]
4. with a single new lesion of the proximal left anterior descending coronary artery ("Italy" trial) [55]
5. chronic coronary occlusion (SICCO, GISSOC and "Britain" trials) [56,57,58]
6. following MI (GRAMI, FRESCO and "Holland" trials) [59,60,61]

Summary results of these trials are shown in Table 2. Further details are shown in Appendix 2

Full published trial reports for three randomised controlled trials were found which did not meet the inclusion criteria for this review. One trial compared stents to PTCA in obstructed coronary artery bypass grafts,[62] another compared stents with no treatment 24 hours after a partially successful PTCA[63] and the third was a trial of abciximab use in stenting compared to abciximab use in PTCA and to stenting without abciximab.[40]

Table 2 Summary of Trials

Trial date published	size	Death	CVA	MI	AFS	EFS	CABG	PTCA	Angina	significant differences ($p<0.05$) found for stent group (vs PTCA)
BENESTENT 1994[45], 1996[46], 1997[24]	516	☑	☑	☑	☑	☑	☑	☑	☑	decreased risk repeat PTCA
STRESS 1994[48],1995[49] 1997[50,53], 1998[51,52,]	407	☑	☑	☑	☑	☑	☑	☑	☒	none
Switzerland 1996[54]	84	☑	☑	☑	☑	☑	☑	☑	☒	none
Italy 1997[55]	120	☑	☒	☑	☑	☑	☑	☑	☒	increased event-free survival
BENESTENT -II 1998 [28]	823	☑	☒	☑	☑	☑	☑	☑	☑	increased event-free survival, decreased repeat PTCA
SICCO 1996[56]	117	☑	☑	☑	☑	☒	☑	☑	☒	increased angina-free survival
GISSOC 1998 [57]	110	☑	☑	☑	☑	☑	☑	☑	☒	decreased recurrent ischaemia and target lesion revascularisation
Britain 1998 [58]	60	☑	☒	☑	☒	☑	☑	☑	☒	none
GRAMI 1998 [60]	104	☑	☒	☒	☒	☑	☒	☑	☒	increased event-free survival
FRESCO 1998 [59]	150	☑	☒	☑	☒	☑	☑	☑	☒	increased event-free survival,decreased PTCA and recurrent ischaemia
Holland 1998 [61]	227	☑	☒	☑	☒	☑	☑	☑	☒	increased event-free survival, decreased MI and target vessel revascularisation

(AFS = angina free survival, EFS = event free survival, Angina = change in angina grades)
☑ = outcome measure reported in trial. ☒ = outcome measure not reported in trial.

6.2 Randomised controlled trials in progress.

There are numerous randomised controlled trials that are currently ongoing or very recently published as meeting abstracts only. The trials reported include:
TASC I -Trial of angioplasty and stents in Canada.[64]
TASC II -Stent vs prolonged perfusion balloon dilatation.[65]
BOSS, OCBAS - Optimal balloon angioplasty vs stents.[66,67.]
PASTA - stents vs PTCA in acute myocardial infarction.[68,69]
STRESS III - stents vs PTCA in larger coronary arteries.[70]
Stent implantation after successful PTCA for chronic coronary occlusion.[71]
Comparison of effectiveness of different stents.[72,73,74]
Because full published reports for these randomised controlled trials are not yet available, they are not included in this review.

Randomised controlled trials in progress comparing elective stenting to CABG include SOS, ARTS, and SIMA trials. Randomised controlled trials in progress comparing antithrombotic treatments include STARS, ISAR and HALL trials.

No randomised controlled trials were found on bailout stenting, stenting in long lesions, small vessels, bifurcation or ostial lesions, or that directly compare the use of stents (following PTCA) with emergency CABG. There were, however, subgroup analyses of larger trials that looked specifically at small vessels.[51,75]

Clinical results of randomised controlled trials for longer than one year are not available.

6.2.1 Evidence from other trials

Longer term clinical results of stent use are not yet well established.[76,77] Although there are some long term studies published, none of these are from randomised controlled trials.[78,79] Also, there is little evidence for repeat stenting for in-stent restenosis.[76]

6.3 Trial design

All of the trials look at patients who could have been treated with either PTCA alone or stents. The use of stents is rapidly changing so current practice does not necessarily correspond with evidence from the recent trials.

Each of these trials has looked at different subgroups of coronary artery disease and patient characteristics. For example, the SICCO, GISSOC and Britain trials just look at coronary artery occlusion whereas the Italy trial specifically excludes patients with coronary occlusion. Eight of the trials use the Palmaz-Schatz stent, the Switzerland and Britain trials use the Wiktor stent, the Britain trial also uses the AVE stent and the GRAMI and FRESCO trials use the Gianturco-Roubin stent. All stents are different sizes and shapes[29]. However, in a small randomised controlled trial which compared Wiktor and Palmaz-Schatz stents, there were no significant differences in adverse endpoint at 6 months follow up between the two groups[80]. This suggests that the results from trials using either of these two stents may be comparable. Results from AVE and Gianturco-Roubin stents may be comparable to Palmaz-Schatz or Wiktor stents[72,73,74].

Neither physicians nor patients were blinded to treatment received any of the trials.

Table 3. Trial Designs

Trial	Randomisation	Early outcomes reported	late angiographic outcomes	late clinical outcomes reported
BENESTENT	Block/ Telephone	In Hospital	6 Months	7 Months & 12 Months
STRESS	Block/Sealed Envelope	0-14 Days	6 Months	15-240 Days
Switzerland	Not Specified	In Hospital	6 Months	Discharge to 6 Months
Italy	Not Specified	In Hospital	6 Months	12 Months
BENESTENT -II	Block/ Telephone	1 Month	6 Months	12 Months
SICCO	Block/Sealed Envelope		6 Months	14-180 Days & to 300 Days
GISSOC	Sealed Envelope	In Hospital	9 Months	9 Months
Britain	Not Specified	In Hospital	6 Months	6 Months
GRAMI	Not Specified	In Hospital (0-30 Days)	Not Given	12 Months
FRESCO	Sealed Envelope	0-30 Days	6 Months	6 Months
Holland	Sealed Envelope	In Hospital	Not Given	6 Months

6.3.1 Baseline characteristics

Within each trial the baseline characteristics of control and treatment groups were similar except in the STRESS trial where there were significantly more male patients in the stent group. In the GISSOC trial, 40% more patients in the PTCA group had previous MI. Each of the trials had different exclusion criteria.

Table 4. Baseline clinical characteristics at the start of the trials.

Trial	stable angina %	unstable angina %	previous MI %	sample size
BENESTENT	100	0	19.4	516
STRESS	52-53	47-48	36.5	407
Swiss	85.7	14.3	36.8	84
Italy	82-83	17-18	26.5	120
BENESTENT-II	50-53	40-45	25-28	823
SICCO	Not Given	Not Given	62.4	117
GISSOC	80.7-92.3	7.1-11	54-83	110
Britain	Not Given	Not Given	Not Given	60
GRAMI	Not Given	Not Given	6-15	104
FRESCO	Not Given	Not Given	8	150
Holland	Not Given	Not Given	13	227

6.3.2 Drop out and follow up

In the SICCO, GISSOC, Britain, GRAMI, FRESCO and Holland trials, randomisation was only carried out after a successful PTCA whereas in the other five trials randomisation was carried out before intervention. In the BENESTENT, STRESS, BENESTENT-II, SICCO and GISSOC trials the few patients who dropped out after randomisation were not included in the results and analysis. Only in the Italy trial were they included in the analysis. In the other five trials there were no dropouts after randomisation.

In the STRESS trial, the significance test for target vessel revascularisation rate at 8 month follow up between the PTCA and stent groups was p=0.06. This was taken as evidence that stenting reduces the need for subsequent revascularisation.[48] In the STRESS trial at one year follow up there was no statistical significance for revascularisation rate between the PTCA and stent groups.[52] In the Switzerland trial, for the patients undergoing repeat angioplasty and CABG in the PTCA arm of the trial, the numbers do not correspond between table II and text. In the Holland trial the clinical outcome numbers do not

correspond between Figure I and text. No angiographic follow up was carried out in the GRAMI and Holland trials.

Table 5. Drop out, switch of treatment/treatment failure and angiographic follow up rates.

	drop out rates (%)		treatment failure/switch (%)		angiographic follow up (%)	
	PTCA	Stent	PTCA	Stent	PTCA	Stent
BENESTENT	0.4	1.1	6.2	9.3	combined	93
STRESS	0.5	1.0	10.4	3.9	78	86
Switzerland	0	0	7.1	4.8	95	95
Italy	3.3	3.3	6.9	5.2	79	84
BENESTENT -II	0.2	0.7	13.9	17.9	combined	92
SICCO	combined	1.7	0	1.7	97	98
GISSOC	1.8	0	1.9	0	87	89
Britain	0	0	0	0	97	93
GRAMI	0	0	32.7	1.9	0	0
FRESCO	0	0	0	0	95	94
Holland	0	0	13.0	1.8	0	0

6.4 Clinical results

This report concentrates on the clinical outcomes, as opposed to angiographic outcomes, as these are the most relevant to the subsequent cost/utility analysis presented later in the report.

The clinical outcomes measured included death, CVA, acute myocardial infarction, event free survival, presence of angina on follow up and need for CABG or repeat PTCA. Bleeding and vascular complications and duration of hospital stay are also reported but are not used in the cost/utility analysis because of changes in anticoagulation treatment since these trials were carried out. Clinical results are tabulated in Table 8 and Appendix 2.

Immediate clinical results.

There were no significant differences between PTCA and stent groups in death rates, incidence of cerebrovascular accident, myocardial infarction (Q wave and non Q wave combined) or need for CABG in any of the trials. There were significant increases for the stent group in the BENESTENT, STRESS, Switzerland, Italy and SICCO trials in mean length of hospital stay and for bleeding complications. There were increased bleeding complications (but not significantly different) in the BENESTENT-II, GISSOC, Britain and

Holland trials and no difference in the GRAMI and FRESCO trials. There was a longer hospital stay for the stent group in the BENESTENT-II, Britain GRAMI and Holland trials and which was a statistically significant increase in the GISSOC trial.

Long term clinical results.

There is no published evidence from controlled trials on follow up of patients for longer than one year.

For the eleven RCTs reviewed there were no significant differences between PTCA and stent groups in death rates, incidence of cerebrovascular accident, or need for CABG in any of the trials. There was a significant difference in the incidence of acute MI in the Holland trial only. There was a significant difference in the need for repeat PTCA in the BENESTENT, BENESTENT-II, SICCO, and FRESCO trials but not in the other five trials that reported repeat PTCA.
For composite end points reported (repeat intervention or target vessel revascularisation and event free survival), there was a significantly decreased rate of repeat intervention for the stent group in the GISSOC, FRESCO and Holland trials only. (This repeat intervention was mainly the need for repeat PTCA). In the SICCO trial there was a significant difference between the stent and PTCA groups for repeat intervention between 180 days and 300 days but not between 14 days and 180 days. In a subgroup analysis of the STRESS I and II combined trial, investigating smaller vessels, there was a significant decrease in the stent group for target vessel revascularisation but not for repeat PTCA[51].
There were significant differences in event free survival shown in the BENESTENT, Italy, BENESTENT-II, GRAMI, FRESCO and Holland trials but not in the STRESS or Switzerland trials, again this was mainly affected by the need for repeat PTCA within the follow up period. The STRESS and Switzerland trials showed no significant differences (to $p<0,05$) in any of the outcome measures.

Table 6. Reintervention rates for the eleven trials.

Trial	PTCA group			Stent group		
	CABG %	PTCA %	TVR	CABG %	PTCA %	TVR
BENESTENT	5.0	20.6***	NG	6.9	10.0***	NG
STRESS	8.9	20.8	17.3#	5.8	19.0	11.7#
Switzerland ++	2.3	16.7	19.0	7.1	11.9	19.0
Italy	1.7	11.7	21.7	1.7	5.0	6.7
BENESTENT-II	1.5	15.6*	NG	1.9	9.4*	NG
SICCO	1.7	40.7	42.4*	5.2	17.2	22.4*
GISSOC	7.4	18.5	22.2**	3.6	5.4	5.4**
Britain	6.7	16.7	NG	3.3	10.0	NG
GRAMI	NG	NG	19.2	NG	NG	13.5
FRESCO	2.7	22.7**	25.3**	0	6.7**	5.4**
Holland ++	NG	NG	16.5**	NG	NG	3.6**

*= statistically significant to p<0.05, ** to p< 0.01, *** to p<0.001
TVR = target vessel revascularisation (CABG and/or PTCA). # - symptom driven TVR only.
++ - numbers given in the text of the paper differ from those given in the figures. Numbers from the figures have been used here.

There were no significant differences in number of patients with angina on follow up in the BENESTENT, STRESS and Switzerland trials but in the Italy, SICCO and GISSOC trials, for the stent group of patients, significantly fewer had recurrence of angina on follow up.

Table 7 Angina free status on follow up for the eleven trials.

	sample size	PTCA	%	sample size	Stent	%	
BENESTENT	257	218	84.8	259	210	81.0	p=NS
STRESS	155	130	83.9	161	135	83.9	p=NS
Switzerland	42	35	85.4	42	36	83.4	p=NS
Italy	60	45	75.0	60	54	90.0	p=0.05
BENESTENT-II*	410	281	68.5	413	314	76.0	p=NG
SICCO	59	14	24.0	58	33	57.0	p<0.001
GISSOC[#]	54	28	51.9	56	48	85.7	p=0.002
Britain	30	NG		30	NG		
GRAMI	52	NG		52	NG		
FRESCO	75	NG		75	NG		
Holland	115	NG		112	NG		

* at 6 months. NS = not significant. NG = not given. # - includes asymptomatic ischaemia.

Table 8. Long term clinical results

BENESTENT sample size	follow up	death	CVA	MI	CABG	PTCA	Event free survival
PTCA 257	12 mths	2 (0.8%)	2 (0.8%)	11 (4.3%)	13 (5.0%)	53 (20.6%)*	176 (68.5%)*
stent 259		3 (1.2%)	0	13 (5.0%)	18 (6.9%)	26 (10.0%)*	199 (76.8%)*

STRESS sample size	follow up	death	CVA	MI	CABG	PTCA	Event free survival
PTCA 202	12 months	4 (2.0%)	not given	16 (7.9%)	18 (8.9%)	38 (19.0%)	141 (69.8%)
stent 205		3 (1.5%)		13 (6.3%)	12 (5.8%)	43 (20.8%)	154 (75.1%)

Switzerland sample size	follow up	death	CVA	MI	CABG	PTCA	Event free survival
PTCA 42	6 months	0	0	0	1 (2.3%)	7 (16.7%)	31 (73.8%)
stent 42		0	1 (2.3%)	0	3 (7.1%)	5 (11.9%)	32 (76.1%)

Italy sample size	follow up	death	CVA	MI	CABG	PTCA	Event free survival
PTCA 60	12 months	1 (1.7%)	0	3 (5.0%)	1 (1.7%)	7 (11.7%)	40 (66.7%)*
stent 60		1 (1.7%)	0	2 (3.3%)	1 (1.7%)	3 (5.0%)	52 (86.7%)*

BENESTENT -II sample size	follow up	death	CVA	MI	CABG	PTCA	Event free survival
PTCA 410	12 months	4 (1.0%)	not given	18 (4.4%)	6 (1.5%)	64 (15.6%)*	318 (77.6%)*
stent 413		4 (1.0%)		14 (3.4%)	8 (1.9%)	39 (9.4%)*	348 (84.3%)*

SICCO sample size	follow up	death	CVA	MI	CABG	PTCA	Event free survival[#]
PTCA 59	6 months	0	0	0	1 (1.7%)	24 (40.7%)*	not given
stent 58		0	0	1 (1.7%)	3 (5.2%)	10 (17.2%)*	

GISSOC sample size	follow up	death	CVA	MI	CABG	PTCA	Event free survival
PTCA 54	9 months	1 (1.9%)	not given	0	4 (7.4%)	10 (18.5%)	not given
stent 56		0		0	2 (3.6%)	3 (5.4%)	

Britain sample size	follow up	death	CVA	MI	CABG	PTCA	Event free survival
PTCA 30	6 months	1 (3.3%)	not given	1 (3.3%)	2 (6.7%)	5 (16.7%)	21 (70.0%)
stent 30		0		0	1 (3.3%)	3 (10.0%)	26 (86.7%)

GRAMI sample size	follow up	death	CVA	MI	Target vessel revascularisation	Event free survival
PTCA 52	12 months	4 (7.7%)	not given	not given	10 (19.2%)	34 (65.4%)*
stent 52		2 (3.8%)			7 (13.5%)	43 (82.7%)*

FRESCO sample size	follow up	death	CVA	MI	CABG	PTCA	Event free survival
PTCA 75	6 months	4 (5.3%)	not given	2 (2.7%)	2 (2.7%)	17 (22.7%)*	not given
stent 75		1 (1.3%)		1 (1.3%)	0	5 (6.7%)*	

Holland sample size	follow up	death	CVA	MI	Target vessel revascularisation	Event free survival[Φ]
PTCA 115	6 months	3 (2.6%)	not given	8 (7.0%)*	19 (16.5%)*	95 (82.6%)*
stent 112		2 (1.8%)		1 (0.9%)*	4 (3.6%)*	107 (95.5%)*

(* = $P < 0.05$). [#] Event free survival reported here as cumulative incidence not actuarial survival.
[Φ] Numbers taken from figure not text.

6.5 Angiographic results

The randomised controlled trials reviewed all show significant differences in angiographic results between the stent group and the PTCA group immediately post intervention. This confirms numerous angiographic studies from observational and non-randomised trials which suggest that stent implantation achieves consistently superior increases in lumen diameter compared to PTCA.[81,82,83,84] On follow up the angiographic results do not show quite such consistent differences. Angiographic results do not correlate well with clinical improvement[24].

Table 9. Angiographic follow up results for stent group vs. PTCA.

	Minimal Lumen Diameter	%Stenosis	Rate of Restenosis >50%
BENESTENT	No Difference	Less (++)	Lower (+)
STRESS	Bigger (++)	Less (++)	Lower (+)
Switzerland	No Difference	No Difference	No Difference
Italy	Bigger (+)	Less (++)	Lower (++)
BENESTENT-II	Bigger(+++)	Less (+++)	Lower (+++)
SICCO	Bigger (+++)	Less (+++)	Lower (+++)
GISSOC	Bigger(+++)	Less (+++)	Lower (+++)
Britain	Bigger(+)	Less (++)	Lower (++)
GRAMI	No Follow Up		
FRESCO	Bigger(+)	Not Given	Lower (+)
Holland	No Follow Up		

(+= statistically significant to $p<0.05$, ++ to $p< 0.01$, +++ to $p<0.001$)

6.6 Meta-analysis of clinical results

(* put in 4 pages of Stentmet1.doc*) (*found in HSDEC*)

editorials in the medical literature.[85,86,87,88,89]

6.7 Economic evidence

Numerous economic analysis studies were found. These can be separated into several distinct groups.

1. Cost effectiveness studies comparing stents to PTCA using RCT evidence.[21,28,49,90]
2. Cost utility studies comparing stents to PTCA using RCT evidence.[91]
3. Cost utility studies comparing stents to PTCA using non-RCT evidence.[92]
4. Cost effectiveness studies comparing stents with anticoagulation to stents without or comparing stents to PTCA or other treatments using non-RCT evidence.[93,94,95]
5. Analysis of economic studies of stent, PTCA, CABG and medical treatment.[9,25,27,30,39,96,97]
6. Other cost effectiveness studies that may be relevant eg PTCA compared to CABG.[7,98,99,100,101]

Groups 1, 2 and 3 have been tabulated as they are the most relevant to this report. The different methodologies used mean that comparison between cost effectiveness studies is not possible (except between the two BENESTENT studies). Only the BENESTENT-II trial included costs as part of the trial design. The study based on the STRESS trial is an in depth cost analysis and very little is included about effectiveness. The SHPIC[21] report states that it uses preliminary results from both RCTs available at that time but does not show how the results were combined. A limited sensitivity analysis is included, based on some of the assumptions made in the cost effectiveness calculations. The cost utility study using non-RCT evidence[92] uses numerous references on which to base its conclusions but no RCT results were available when it was written. How results from the non-RCT studies were combined is not stated. The cost utility study using RCT evidence is based primarily on the BENESTENT study but also includes data from the STRESS, Swiss, Italy and SICCO studies. Both these studies include sensitivity analyses

Table 10. Cost effectiveness studies using RCT evidence

Trial analysis based on	Time duration	No of pts	Cost estimation	Calculation	Notes
BENESTENT Van Hout[90] 1996	7 mths	516 (719)	Direct medical costs only Unit costs estimated from one hospital	average 1year cost per stent patient - average 1 year cost per PTCA patient / %age reduction in EFS at 1 year	Includes some data from BENESTENT-II pilot trial as comparison ()
STRESS Cohen[49] 1995	1 yr	207	Itemised billing per patient (99% complete follow up), costs from a mixture of 'bottom -up', 'top down' and average cost methods	costs calculation only, not combined with effectiveness measurement	substudy, inclusion of patients dependent on hospital where treatment took place
BENESTENT-II Serruys [28] 1998	1 yr	406	Costs = patient's resource use (from notes) x unit cost. Unit costs estimated from one hospital	1.average 1year cost per stent patient - average 1 year cost per PTCA patient / %age reduction in EFS at 1 year. 2.average costs per patient /% EFS, calculated for PTCA and stent group	clinical follow up group only used for cost effectiveness study
BENESTENT and STRESS SHPIC[21] 1996	7 mths (BENESTENT) and 6 mths (STRESS)	930	Estimated from prices from a range of UK hospitals	Cost per second procedure avoided	Early results of trials combined.

EFS=event free survival.

Table 11. Cost utility studies using RCT[91] and non-RCT evidence[92]

Study	Studies analysis based on	Time dura-tion	QALY calcul-ation	Cost estimation	Calculation	Notes
Chase and Best [91]	BENE STENT,	1 year	Based on symptomatic restenosis rate	Averaged cost differences between stent and PTCA between two hospitals in South and West Region, GB.	-quality adjusted life years, treatment cost, -incremental cost per QALY gained	DEC report with prescribed format. Method used clearly stated. Sensitivity analysis performed.
Cohen and Breall 1994[92]	45 registry and case series	various up to 10 years	Based on event free survival rates	measured resource use for each procedure or service, average cost per patient, costs discounted at 5% per year	-quality adjusted life expectancy, -lifetime treatment cost, -incremental cost per QALY gained	uses Markov (state transition) model, extensive sensitivity analysis, method used clearly stated

Table 12. Results of cost effectiveness studies

Trial analysis based on		average costs per patient	effective-ness	cost per event free survivor	additional cost per additional event free survivor	notes
BENESTENT Van Hout[90]	PTCA stent	Dfl 15,208 Dfl 23,593	70.43% 79.92% EFS	Dfl 21,593 Dfl 29,520	Dfl 88,315 (£28,500)	includes 95% probability ellipses
STRESS Cohen[49]	PTCA stent	US$10,865 US$11,656	35 19 repeat revasculari sations. (numbers of patients)	not calculated	not calculated	costs given with standard deviations
BENESTENT - II Serruys [28]	PTCA stent	Dfl 16,727 Dfl 18,812	79% 89% EFS	Dfl 21,309 Dfl 21 073	Dfl 19,358 (£6,200) (used direct costs only)	numerous calculations unclear in text
BENESTENT and STRESS SHPIC[21]	PTCA stent	excess cost of 57%	24% 17% reduced need for 2nd procedure	not calculated	£20,700 (cost per second procedure avoided)	Unclear how cost per second procedure avoided calculated

EFS=event free survival. DFl=Dutch Florins

The SHPIC report calculated the cost per second procedure avoided rather than additional cost per additional event free survivor. Therefore, this result is not comparable to the two BENESTENT trials. Results calculated in the Netherlands, USA and Britain in different years are also difficult to compare. Additional costs per additional event free survivor results in the cost effectiveness and cost utility studies have been converted to £ sterling using exchange rates of DFl3.1 and US$1.6 to £1.00 (November 1998 exchange rates). In the BENESTENT11 trial the cost effectiveness calculations as published contain so many discrepancies that it brings their results into question. No explanation of the meaning of direct costs only was given.

Table 13. Result of cost utility study[92]

Trial	Cost difference per patient	Difference in quality adjusted life expectancy per patient	Additional cost per additional event free survivor	Sensitivity analysis
Chase and Best [91]	£1,431	0.0053	£250,000	£20,000-£772,000
Cohen and Breall 1994[92]	US$600	0.04	US$23,600 (£14,750)	US$13,600-US$121,000 (£8,500-£75,600)

The sensitivity analysis in the Cohen and Breall study[92] indicated that the cost effectiveness was most sensitive to variations in relative restenosis rates of stenting and PTCA. It was also highly sensitive to the cost of stenting and the rate of emergency CABG. The difference in additional cost per additional QALY between the two cost utility studies may be due to the difference in method of calculation of the QALYs. Also the costs of stents have changed over the last 4 years has changed.

7. Economic analysis

7.1 Benefits and disbenefits for Stents v. PTCA

Data from the BENESTENT 11 trial[28] is used to give an estimate of the relative benefits of using stents compared to PTCA. This trial has been used because:

1. It is the largest trial
2. It has recently been reported
3. It meets the inclusion criteria
4. Outcomes are clearly reported
5. It includes a wide mix of patients with both stable and unstable angina graded according to the Canadian Cardiovascular Society (CCS) Grading of Angina of Effort and the Braunwald Classification of unstable angina.(see Appendix 1). Patients are graded before treatment and at 6 months follow up
6. It includes a subgroup analysis of patients assigned to clinical follow up alone compared to angiographic and clinical follow up.

The disadvantage of this trial is that it used heparin coated stents. This may not mirror current practice. It is acknowledged that the strict inclusion criteria for RCTs mean that lesions must be suitable for both PTCA and stenting, which may not represent lesions treated in clinical practice. In this RCT all patients were also suitable for CABG.

The clinical descriptions in the CCS and Braunwald classifications were used to estimate EUROQOL scores for each angina grade (see Table 14 and Appendix 3).

Table 14. EUROQOL scores from CCS and Braunwald classifications of angina.

angina grade	EUROQOL score	EUROQOL dimension	range
silent ischaemia	0.919	11111	1.000-0.848
CCS grade I	0.883	11211	0.919-0.812
II	0.760	11221	0.883-0.689
III	0.587	22221	0.691-0.516
IV	0.260	22321	0.587-0.189
Braunwald 1ABC	0.691	21221	0.760-0.620
2ABC	0.516	22222	0.656-0.189
3ABC	0.073	32221	0.587-0.002

In the BENESTENT11 trial the primary clinical endpoint was a composite of death, MI, CABG or a repeat PTCA at the previously treated lesion at 6 months follow up. Repeat PTCA for lesions in other coronary arteries were not recorded as an endpoint in the trial. The secondary endpoints included anginal functional class at 6 months, major bleeding complications and vascular complications that necessitated surgical intervention or blood transfusion.

To calculate benefits in Quality Adjusted Life Years (QALYs) the outcomes used are death, angina functional class and repeat PTCA. Death was included in the calculation, even though there was no statistical significance between the PTCA and stent groups, in order to compare the mortality of the trial patients if they had been treated medically or with CABG instead of with PTCA or stent.

To calculate the benefits of using stents or PTCA on patients, a baseline measure of what would have happened if those patients had been treated with medical therapy needs to be established. It is acknowledged that PTCA and stents are not alternatives to medical therapy but are used when this has failed to control symptoms. However, medical therapy is the best baseline comparison group available.

7.1.1 Baseline measure

The CCS and Braunwald grading of angina for both the PTCA and stent groups were given at the start of the trial. This is used to give the average adjusted QALY for the patients at the start of the trial.

- The mean QALY per patient at the start of the trials is 0.651. This is calculated from tables 15 and 16.

Table 15. Group angina grades at start of trial

Angina grade	PTCA group before treatment	Stent group before treatment	Combined groups before treatment (%)	
silent ischaemia	29	22	51	(6.2)
CCS grade I	31	15	46	(5.6)
II	103	95	198	(24.1)
III	77	91	168	(20.4)
IV	6	6	12	(1.5)
Braunwald 1ABC	52	52	100	(12.2)
2ABC	131	131	246	(29.9)
3ABC	0	0	0	
subtotal	409	412	821	
missing data	1	1	2	
total	410	413	823	

Table 16. Calculation of IHQL score - before treatment

angina grade	% patients	EUROQOL score	Total	QALY per patient
silent ischaemia	6.2	0.919	5.7	
CCS grade I	5.6	0.883	4.9	
II	24.1	0.760	18.3	
III	20.4	0.587	12.0	
IV	1.5	0.260	0.4	
Braunwald 1ABC	12.2	0.691	8.4	
2ABC	29.9	0.516	15.4	
3ABC	0	0.073	0	
missing	0.2	0		
total			65.1 /100 =	0.651

Note

Silent ischaemia means that the patient has no angina. Clarification was sought from the BENESTENT trialists[102] regarding the physical state of the patients with no angina and reasons for their inclusion in that trial. The trialists suggested that the patients had non-exertional or mixed angina but not unstable angina. It is likely that the patients with silent ischaemia who were in the BENESTENT-II trial had other evidence of coronary artery disease such as a previous myocardial infarction or a strongly positive exercise test which had resulted in cardiac investigations being undertaken. Stenosed coronary arteries found on angiography resulted in patient inclusion into the trial despite the lack of angina. Anginal symptoms do not correlate well with myocardial ischaemia.[103]

7.1.2 Medical treatment

At the end of one year on medical treatment, approximately 40% of patients would be angina free, 2% would have died and 58% would have stable angina (see notes below). From this the average adjusted QALY score for all patients taking part in the BENESTENT-II trial, if they had been treated medically instead of with PTCA or stent, can be calculated.

- The mean QALY score per patient after one year's medical treatment is 78.4/100 = 0.784

Table 17. Calculation of QALY score after medical treatment

category	% patients	EUROQOL score	Time span over 1 year (in years)	Total per 100 patients
died	2.0	0.651	0.5	0.6
stable angina	58.0	0.651	1	37.8
angina free	40.0	1.000	1	40.0
Total				78.4

7.1.3 Notes

Angina Status

In a recent, large randomised controlled trial (N=328) of medical treatment versus PTCA[104] in male patients with either single or double vessel disease, 48% of patients with single vessel disease and 36% with double vessel disease treated in the medical arm of the trial were angina free at 6 months. In a similar, smaller trial of medical treatment versus PTCA in single vessel disease only,[105] 46% of patients who had been treated medically were angina free at 6 months. The baseline clinical characteristics of the patients in the BENESTENT-II trial (where previous conditions include myocardial infarction (26.2% patients), CABG (1.7%) and PTCA (7.3%)) suggests these patients had a mixture of single and multiple vessel disease. Therefore it is assumed that approximately 40% patients would have been angina free if they had received medical treatment. The level of 30 - 40% spontaneous remission of angina for 2 or more years is also suggested in a review by Cleland.[7]

The relative spread of angina severity according to CCS classification for this group of patients after one year on medical treatment is assumed to be the same angina spread as before treatment.

Mortality

It is assumed that the mortality rate for those patients involved in the trial would have been 2% if they had been treated medically. This figure is estimated from data from several randomised controlled trials comparing medical treatment to PTCA.[26,104,105,106,] For the purposes of this model it is assumed that all patients who die during the year, do so at 6 months.

7.1.4 PTCA and stent treatment outcomes

In order to calculate the change in QALY scores over 1 year, EUROQOL scores for patients with angina between intervention and 1 year and the percentages of patients in each category (angina free, with angina, dead etc) are required. (see footnote [1]). Unfortunately, angina grades are only given at 6 months. Therefore the QALY scores are calculated for six months and then doubled.

In the BENESTENT-II trial, 1.0% of the PTCA group and 1.0% of the stent group died during the follow up period. At six months follow up the number of patients who are angina free in the PTCA and Stent groups are shown in table 18. The proportion of patients who had a repeat PTCA were 20.6% in the PTCA group and 10.0% in the stent group. (see footnote [2])

Table 18 Angina grades at 6 months follow up.

Angina grade	PTCA group after treatment (% patients)	Stent group after treatment (% patients)
angina free	68.5	76.0
silent ischaemia	2.7	1.7
CCS grade I	6.6	5.8
II	9.3	10.2
III	4.4	2.4
IV	0.2	0
Braunwald 1ABC	1.2	0.7
2ABC	1.7	0.7
3ABC	4.1	1.7

[1] For the purposes of this model it is assumed that all repeat PTCA interventions occurred within the first six months.
It has been suggested by a local expert in stent insertion that the intervention experience is now very similar from a patient's point of view whether a stent is inserted or not during a PTCA procedure. Therefore it has been estimated that the EUROQOL score for the PTCA and stent procedures would be the same. For the initial and subsequent PTCA / stent procedures an EUROQOL score of 0.300 was estimated for the one week that the invasive procedure takes place.

[2] 13.4% of the PTCA group received a stent and 1.7% of the stent group received PTCA but no stent. The angina grades and repeat intervention rates are given on an intention to treat basis.

7.1.5 PTCA Group QALY calculation

For the PTCA group of patients, over the course of one year, 1.0% died and 99.0% survived.

- The average EUROQOL score per patient *with angina* from intervention to 6 months = 0.661. This is calculated from angina grades given in table 18. The calculation is shown below in table 19. The EUROQOL score is then used to calculate the average QALY per patient over 6 months. (Table 20)

- The average QALY per patient for all PTCA patients over 6 months is 0.432.
- The average QALY per patient for all PTCA patients over 1 year = 0.432 x 2 = 0.863

Figure 8. Flow Diagram of percentages of PTCA patients in each category.

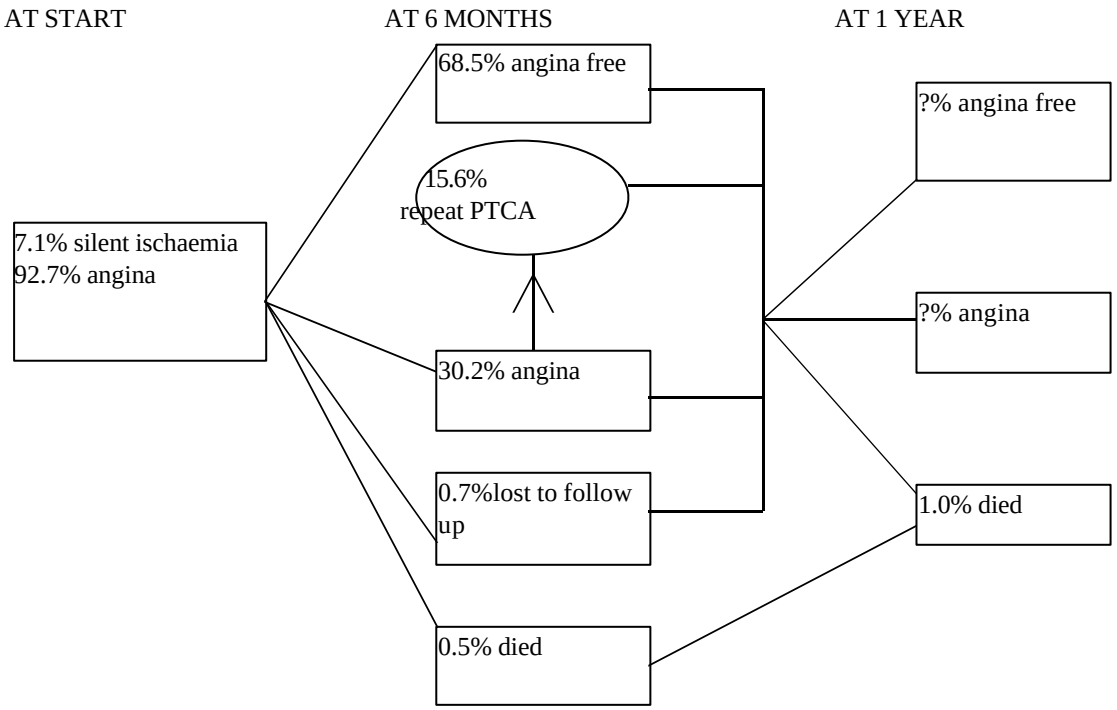


Table 19. Calculation of EUROQOL score from angina grades at 6 months.

angina grade	% patients	EUROQOL score	
silent ischaemia	2.7	0.919	2.5
CCS grade I	6.6	0.883	5.8
II	9.3	0.760	7.0
III	4.4	0.587	2.6
IV	0.2	0.260	0.1
Braunwald 1ABC	1.2	0.691	0.8
2ABC	1.7	0.516	0.9
3ABC	4.1	0.073	0.3
totals	30.2		20.0
lost to follow up	0.7	0	
angina free	68.5	1.000	
died	0.5	0	

The average EUROQOL score for PTCA patients *with angina* between intervention and 6 months is 20.0/30.2 = 0.661

Using this data it is possible to show the QALY scores for the various sub-groups of PTCA patients.

Table 20. Calculation of QALY for PTCA group

	% patients	QALY	time span over 6 months (in weeks)	totals
initial PTCA	100	0.300	1/52	0.6
died	0.5	0.661	25/52	0.2
angina free	68.5	1.000	25/52	32.9
angina with no repeat PTCA	14.6	0.661	25/52	4.6
repeat PTCA	15.6	0.300	1/52	0.1
angina with repeat PTCA	15.6	0.661	24/52	4.8
Total				43.2

Those not accounted for in this block diagram are 3 patients lost to follow up at 6 months. These were assigned no QALYs

Total QALY per patient for the PTCA group over 6 months = 43.2/100 = 0.432

7.1.6 Stent Group QALY calculation

For the stent group of patients, over the course of the year, 1.0% died and 99.0% survived.

- The average EUROQOL score per patient *with angina* from intervention to 6 months = 0.724. This is calculated from angina grades given in table 18. The calculation is shown below in table 21. The EUROQOL score is then used to calculate the average QALY per patient over 6 months. (Table 22)

- The average QALY per patient for all stent patients over 6 months is 0.452.
- The average QALY per patient for all stent patients over 1 year = 0.452 x 2 = 0.903

Figure 9. Flow Diagram of percentages of stent patients in each category.

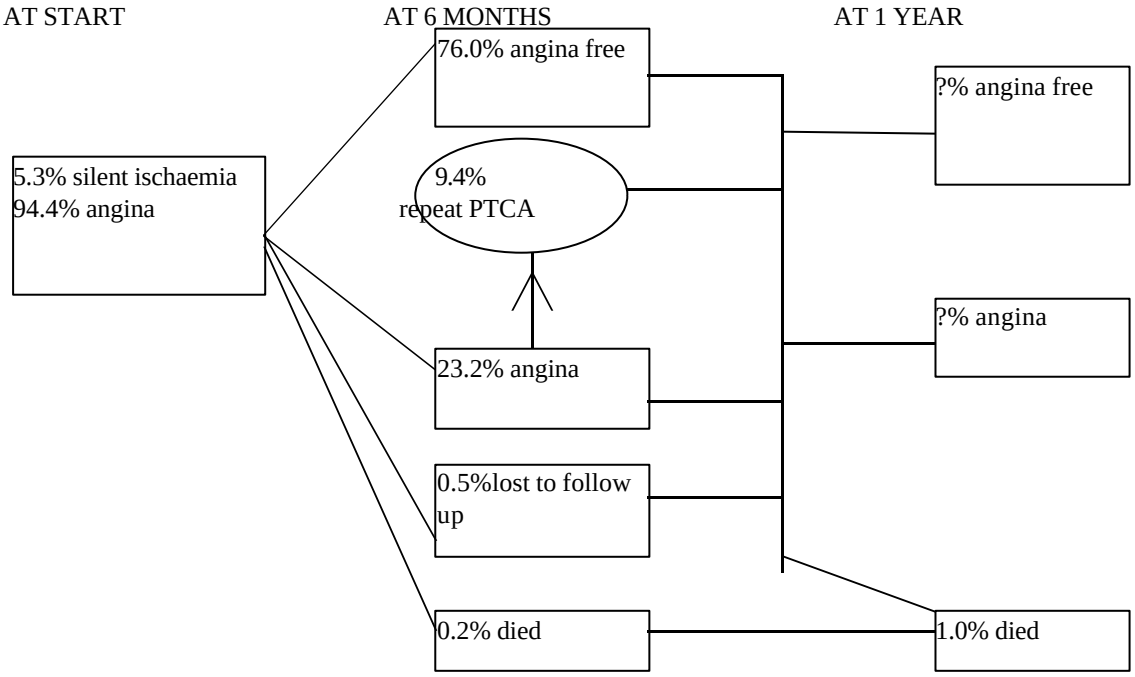


Table 21. Calculation of EUROQOL score from angina grades at 6 months.

angina grade	% patients	EUROQOL score	
silent ischaemia	1.7	0.919	1.6
CCS grade I	5.8	0.883	5.1
II	10.2	0.760	7.7
III	2.4	0.587	1.4
IV	0	0.260	0
Braunwald 1ABC	0.7	0.691	0.5
2ABC	0.7	0.516	0.4
3ABC	1.7	0.073	0.1
totals	23.2		16.8
lost to follow up	0.5	0	
angina free	76.0	1.000	
died	0.2	0	

The average EUROQOL score for PTCA patients *with angina* between intervention and 6 months is 16.8/23.2 = 0.724

Using this data it is possible to show the QALY scores for the various sub-groups of stent patients.

Table 22. Calculation of QALY for stent group

	% patients	QALY	time span over 6 months (in weeks)	totals
initial stent	100	0.300	1/52	0.6
died	0.2	0.724	25/52	0.1
angina free	76.0	1.000	25/52	36.5
angina with no repeat PTCA	13.8	0.724	25/52	4.8
repeat PTCA	9.4	0.300	1/52	0.1
angina with repeat PTCA	9.4	0.724	24/52	3.1
Total				45.2

Those not accounted for in this block diagram are 2 patients lost to follow up at 6 months. These were assigned no QALYs

Total QALY per patient for the stent group over 6 months = 45.2/100 = 0.452

7.1.7 CABG treatment

Over the course of one year, if the trial patients had been treated with CABG instead of with PTCA or stent, approximately 93.5% of patients would have become angina free, 6.2% would have continued to have stable angina or to develop unstable angina and 0.3% would die.

The mean QALY score per patient after CABG for one year is 92.0/100 = 0.920
This is calculated from table 23.

Figure 10. Flow Diagram of percentages of CABG patients in each category.

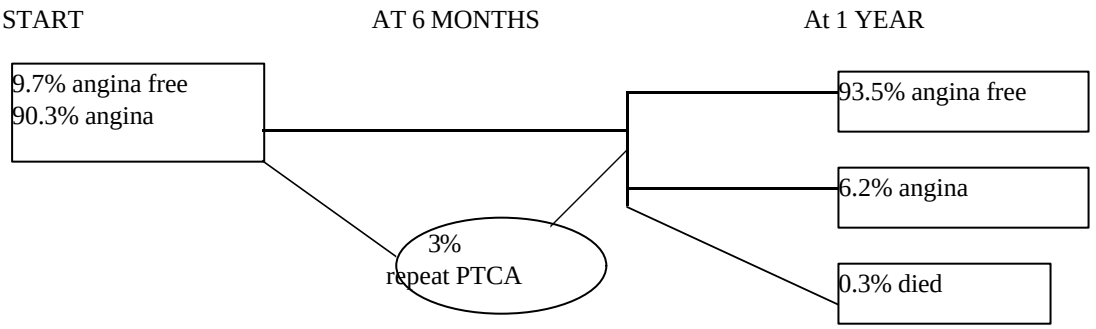


Table 23. Calculation of QALY score - after CABG.

category	% patients	EUROQOL score	time span over 1 year (in months)	totals
after operation	100	0.300	1/12	2.5
died	0.3	0.651	5/12	0.1
stable angina	6.2	0.651	11/12	3.7
angina free	93.5	1.000	11/12	85.7
Total				92.0

7.1.8 Notes

Mortality

A meta-analysis of randomised controlled trials comparing PTCA with CABG includes a sub-analysis of three trials which included patients with single vessel disease only.[15]

Using the combined data for patients in the PTCA arm of this meta-analysis it is possible to compare their results with the results from the PTCA arm of the BENESTENT-II trial.

Table 24. Comparison of results from Benestent-II trial and meta-analysis

	PTCA group (BENESTENT-II trial)	PTCA group (Meta-analysis)	CABG group (Meta-analysis)
Number of patients	823	374	358
deaths in 1 year (%)	1.0	1.9	0.3
angina free (%)	68.5*	85.4	93.5
repeat PTCA (%)	15.6	16.0-30.5	2.2-3.6

* at 6 months

It can be seen that the number of deaths and repeat PTCAs in the PTCA group in the meta-analysis were slightly higher than in the BENESTENT-II trial, but similar. The rates of angina free survival are more difficult to compare. In the BENESTENT trial the 1 year angina free rate for the PTCA group was 84.8% and at 6 months was 65.8%. This suggests that the angina rates between BENESTENT and BENESTENT-II trials are comparable. The 1 year angina free rates in the BENESTENT-II trial may be fairly similar to those in the PTCA group of the meta-analysis. The casemix of patients in the BENESTENT-II trial suggests that their mortality would be low if they had been treated with CABG rather than PTCA or stent.

Angina Status

For those patients still with angina at the end of the follow up year, the grading of angina in patients according to the Canadian Cardiovascular Society grading of angina is not given in the meta-analysis. Therefore, the QALY score used for the patients with angina in Table 24 is the same as the baseline measure.

Effect of Operation

CABG is a major operation and patients take time to recover. In the meta-analysis fewer CABG patients were physically active at 1 month than PTCA patients. By 6 months this had reversed. This was also true of employment status and exercise times. Therefore the average QALY score for the first month after CABG would be low. I have assumed that the patients who died within 1 year have all died at 6 months.

Reintervention

Only approximately 3% of patients had a repeat PTCA. The effect of this on the QALY was too small to merit inclusion.

7.2 Comparison of Treatments

Table 25. The relative benefits for the four treatments (medical, PTCA stent and CABG) over the baseline measure.

	QALY	QALY over baseline measure	QALY over medical treatment
baseline measure	0.651		
medical	0.784	0.133	
PTCA	0.863	0.212	0.079
stent	0.903	0.252	0.119
CABG	0.920	0.269	0.136

These small differences in QALY scores between PTCA and stent scores are very similar to those reported by Cohen et al[92] and Cohen and Baim, as reviewed in the CCOHTA report on coronary stents.[39] A subgroup analysis of the STRESS trial investigating health related quality of life also reported little difference between PTCA and stent groups at 6-18 months after the procedure.[53]

7.3 Costs and savings

The BENESTENT-II trial included data on follow up for one year only. Therefore the costs calculated are just for the year of treatment. Costs are based on data from the BENESTENT-II trial.

7.3.1 Initial hospital costs

Health Service costs include
1. the stay in hospital, including the initial procedure costs and the subsequent complications costs.
2. for the equipment costs of the devices used.
3. The cost of the operation.

In the BENESTENT-II trial, the mean hospital stay was 2.3 days in the PTCA group and 2.8 days in the stent group. The rates of bleeding and vascular complications were low and similar in the PTCA and stent groups (1.0% vs1.2%). Therefore no difference in costs for hospital stay and bleeding complications are assumed between the two groups. The median length of hospital stay duration for PTCA was 3 days in 1995.[22] The trend in hospital stay duration is now decreasing.

The local DHA elective tariffs are assumed to provide approximate costs for PTCA, stent and CABG are below. These include the current costs of hospital stay duration, equipment costs and associated costs.[107] The elective tariff has been used because in the BENESTENT-II trial, all patients were routine admissions. The DHA tariff has been used because the ECR tariff includes an administration charge.

Table 26. Tariffs for treatments

PROCEDURE	TARIFFS			
	DHA elective	ECR elective	DHA emergency	ECR emergency
standard angioplasty	£2,628	£2,930	£2,760	£3,078
angioplasty+stent	£4,054	£4,803	£4,754	£5,300
angioplasty+double stent	£4,808	£5,360	£5,697	£6,353
CABG	£4,825	£5,379	£6,431	£7,171

(cost data from University Hospital NHS Trust 1998)

7.3.2 Costs up to one year

- For the PTCA group, approximately 13.4% of patients received an emergency bailout stent, with the remainder receiving the initial PTCA. During the course of the year, 15.6% had a further PTCA, 1.5% had a CABG and 4.4% had an MI (see table 8). At 6 months, 30.2% of patients continued to have angina. Using data provided by The University Hospital NHS Trust and from Acute Care 95, the approximate costs of treatment for the PTCA group can be calculated.

Table 27. Costs for PTCA.

	%patients	cost (£)	total cost per 100 patients(£)
initial PTCA	86.6	2628	227,585
bailout stent	13.4	4754	63,704
further PTCA (i)	15.6	2628	40,997
CABG (i)	1.5	4825	7,238
MI (ii)	4.4	1225	5,390
angina (iii)	30.2	600	18,120
total cost			363,033

i. Elective tariff.[107] (No data on emergency CABG rates in trial)
ii. Acute myocardial infarction without cardiovascular complications, estimated median cost for those treated in hospital.[22]
iii. Angina aged less than 70 years, estimated median cost for those treated in hospital.[22]

- For the stent group of patients, approximately 1.7% of patients received a PTCA only, with the remainder receiving the initial stent. During the course of the year, 9.4% of patients had a repeat PTCA, 1.9% had a CABG and 3.4% a myocardial infarction. At 6 months 23.2% of the stent group had angina.

Table 28. Costs for single stent.

	%patients	cost (£)	total cost per 100 patients(£)
Initial stent insertion	98.3	4054	398,508
initial PTCA	1.7	2628	4,468
further PTCA	9.4	2628	24,703
CABG	1.9	4825	9,168
MI	3.4	1225	4,165
Angina	23.2	600	13,920
Total cost			454,932

Although in the BENESTENT-II trial only one stent was inserted per patient, in the SICCO, GISSOC, Britain and FRESCO trials more than one stent was inserted in some patients. Insertion of one than one stent is now common practice.[14]

Table 29. Costs for double stent.

	%patients	cost (£)	total cost per 100 patients(£)
Initial stent insertion	98.3	4808	472,626
initial PTCA	1.7	2628	4,468
further PTCA	9.4	2628	24,703
CABG	1.9	4825	9,168
MI	3.4	1225	4,165
Angina	23.2	600	13,920
Total cost			529,048

- If the PTCA group from the BENESTENT-II trial had been treated with CABG then the costs can be estimated, using the data from the meta-analysis of randomised trials comparing CABG to PTCA, using the subgroup analysis for trials of single vessel disease.[17] In this analysis, 2.2-3.6% of the CABG patients had a repeat PTCA during the course of the year following intervention, 1.4% had a repeat CABG and 4.5% had an MI, of whom one patient died. At the end of the first year, 6.5% of patients had angina at grade 2+.

Table 30. Potential costs for CABG

	%patients	cost (£)	total cost per 100 patients(£)
Initial CABG	100	4825	482,500
further PTCA	3.0	2628	7,884
further CABG	1.4	4825	6,755
MI	4.5	1225	5,513
Angina (grade2+)	6.5	600	3,900
Total cost			506,552

7.3.3 Savings with using stents compared to PTCA

1. The number of patients with angina at 6 months follow up in the BENESTENT-II trial, was less in the stent group than in the PTCA group, but the difference was small (not statistically significant), so no savings can be assumed from relief of angina symptoms with stent use as compared to PTCA
2. There were no significant differences between PTCA and stent groups with respect to incidence of death or myocardial infarction. Therefore there are no savings with these events.
3. There were no significant differences between the stent and PTCA groups for the need for CABG.
4. In the BENESTENT-II trial there was a statistically significantly decrease in the number of repeat PTCA procedures performed in the stent group compared to the PTCA group. This could constitute a saving if the patients who would have required a repeat revascularisation had they been treated with PTCA, go on to need no treatment as they have received a stent instead. The numbers needed to treat (NNT) with stent rather than PTCA in order to get one less repeat PTCA is approximately 16. However, in the subgroup analysis of follow up strategies in the BENESTENT-II trial, those who were assigned angiographic follow up had a very similar rate of repeat PTCA and event free survival in the stent and PTCA groups (table 31). In the clinical follow up group (with no angiography), the rate of repeat PTCA was much higher in the PTCA group than the stent group. This is the opposite of the result that would be expected if the rate of repeat PTCA was driven only by objective evidence of restenosis. Therefore it seems likely that in the absence of objective evidence, clinicians' awareness of patients' previous treatment is influencing clinical care decisions. This suggests that repeat PTCA rates used as evidence of effectiveness of stenting compared to PTCA is unreliable. The numbers needed to treat for the two different follow up groups and overall are shown in table 32. The variable rates of repeat PTCA are used in the sensitivity analysis.

Table 31. Variable rates of event-free survival depending on follow up strategy.

Follow up strategy	PTCA group(%)	stent group(%)	
angiographic+clinical	76.6	79.3	p=0.39
clinical only	78.6	89.3	p=0.003

Table 32. Numbers needed to treat and relative risks for the different follow up strategies.

	Complete group	Angiographic+clinical	clinical only
Numbers needed to treat	16.2	21.5	13.4
Relative risk	0.60	0.73	0.44

7.3.4 Sensitivity analysis

The assumptions made in the benefits calculations which are most likely to vary are:
a) clinical effectiveness factors such as the percentages of people with angina at 6 months and the relative percentages of people in the PTCA and stent groups who receive a second PTCA. In the sensitivity analyses, 95% confidence intervals in angina percentages and the subgroup analysis of angiographic and clinical follow up versus clinical follow up only in the rate of repeat PTCA.
b) The quality of life estimates for the different grades of angina in the CCS and Braunwald classification. For the sensitivity analyses the higher and lower EUROQOL score ranges shown at the start of the benefits section of this report are used.

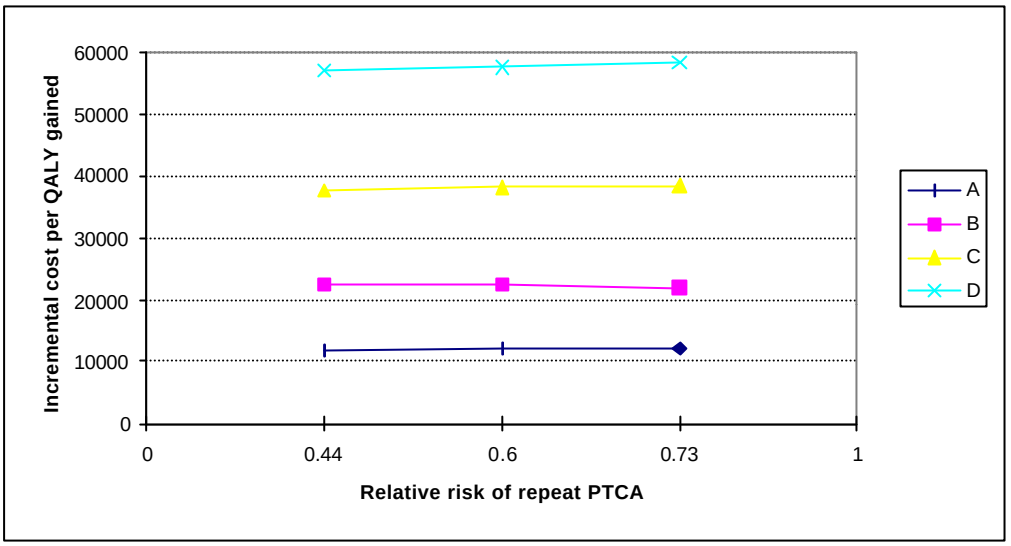
The costs in the cost calculations are based on prices given by one NHS trust. Other NHS trust prices vary widely. The approximate price range for the different procedures from a range of NHS trusts are used for the sensitivity analyses.

Table 33. Range of hospital prices for procedures.

	Low estimate (£)	High estimate (£)
Elective PTCA	1313	2877
Elective single stent	2233	4710
Elective CABG	4825	6416

- The incremental costs per QALY gained for single stent over PTCA were calculated, varying the relative risk for repeat PTCA from 0.44 (clinical follow up only) to 0.73 (angiographic and clinical follow up), keeping all other factors constant. Graph 1 shows that the incremental cost per QALY gained varies very little with the change in relative risk for repeat PTCA.

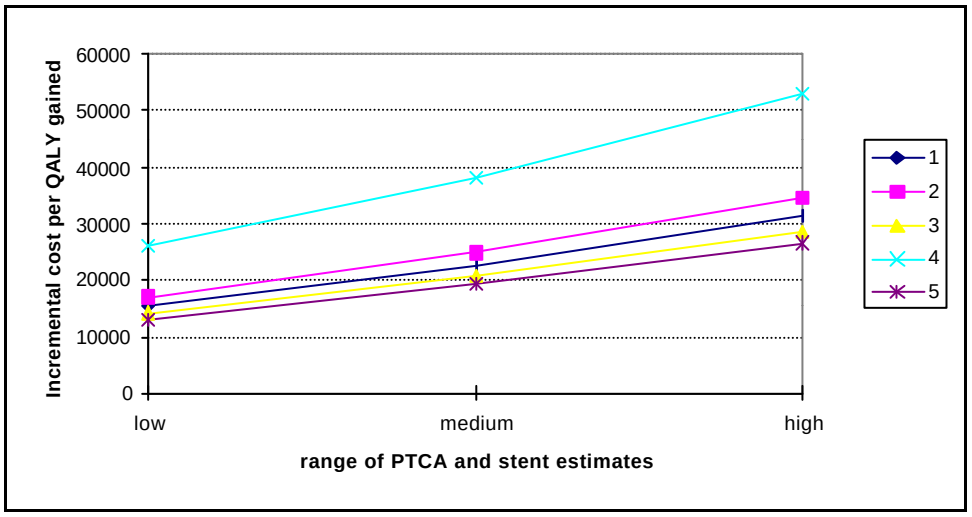
Graph 1. Sensitivity analysis of changes in relative risk for repeat PTCA.



A. Low cost estimates, low angina values, low QALY estimates
B. Normal cost estimates, normal angina values, normal QALY estimates
C. High cost estimates, normal angina values, normal QALY estimates
D. High cost estimates, high angina values, high QALY estimates

- The incremental costs per QALY gained for single stent over PTCA were calculated, varying angina rates and QALY estimates, keeping the relative risk for repeat PTCA and the costs constant. Graph 2 shows that the incremental cost per QALY gained varied with both of these factors.

Graph 2. Sensitivity analysis of changes in angina rates and QALY estimates.



1. Normal angina levels, normal QALY estimates
2. High angina levels, normal QALY estimates
3. Low angina levels, normal QALY estimates
4. Normal angina levels, high QALY estimates

5. Normal angina levels, low QALY estimates

- Varying the costs only and keeping all other factors constant resulted in the incremental cost per QALY gained for single stent over PTCA ranging from £15,268-£30,951.

A recent randomised controlled trial of abciximab,[40] an inhibitor of platelet glycoprotein receptors, has suggested that it may improve survival and reduce need for subsequent revascularisation. Treatment with this drug is very expensive (approximately £840-£1400 per patient). No mention is made of any improvements in angina status with abciximab. When results are compared between the stent+abciximab group and the stent alone group, an improvement of 0.015 QALYs is obtained for the stent+abciximab group. This suggests a very approximate incremental cost per QALY gained for treatment with abciximab of £74,667.

8. Conclusions

- The evidence from the meta analysis suggests that there are some small advantages in stent insertion compared to PTCA for patients groups with new lesions in native coronary arteries, in chronic coronary occlusion and following myocardial infarction.
- There is a decrease in the proportion of patients undergoing a repeat PTCA (relative risk 0.57 in favour of stents) or target vessel revascularisation (PTCA or CABG) (relative risk 0.48) and a slightly better chance of no adverse event (increased event free survival) (relative risk 1.11) in the year following the initial stent insertion. However, the subgroup analysis from the BENESTENT-II trial suggests that these proportions are greatly affected by the clinician's knowledge of the patient's previous treatment.
- The meta analysis shows that the stent group had a slightly better chance of being angina free (relative risk 1.09) at the end of the trials compared to the PTCA group. Benefits may be much greater for patients with chronic coronary occlusion. It is unknown whether this effect would be maintained for longer than one year following stent insertion.
- Evidence from the economic analysis of the BENESTENT-II trial shows that the quality adjusted life years gained from stent insertion is very similar to that from PTCA, in spite of the difference in numbers of repeat interventions performed. This is also suggested by the cost utility study reviewed in the economic evidence section.
- There are fairly large differences in costs between stent and PTCA, particularly if more than one stent is inserted (see tables 34 and 35).
- The cost per QALY gained estimates are restricted to one year only. If benefits of treatment last longer then the estimated costs per QALY gained would be reduced.

Table 34. Costs per QALY gained for PTCA, stent and CABG.

	Cost for one patient (£)	QALY	QALYs gained over baseline measure	cost per change in QALY
medical	600	0.784	0.133	£4,511
PTCA	3,630	0.863	0.212	£17,123
Single stent	4,549	0.903	0.252	£18,052
double stent	5,290	0.903	0.252	£20,992
CABG	5,066	0.920	0.269	£18,833

Table 35. Incremental costs per QALY gained for PTCA stent and CABG.

Comparison	Change in QALY	Change in cost	Change in cost per change in QALY
Single stent over PTCA	0.040	919	£22,975
Double stent over PTCA	0.040	1660	£41,500
CABG over PTCA	0.057	1436	£25,193
CABG over single stent	0.017	517	£30,411
CABG over double stent	0.017	- 224	- £13,177

- The wider issue is not simply to do with the relative cost effectiveness of stents vs PTCA but to the choice between medical and surgical interventions. Much of this choice will depend on patient preference and how they are advised by the clinician that they consult.
- It is important to bear in mind that these costs per quality of life year gained are calculated from evidence provided by the BENESTENT-II trial, where stents and PTCA are assumed to be used appropriately. If intervention procedures are used inappropriately this will increase total treatment costs and certainly increase cost per unit benefit.
- The cost per QALY estimates refer only to patients undergoing elective stent insertion where the initial PTCA has provided reasonably good angiographic results. They also refer to patients with single new lesions of native coronary arteries and where a Palmaz-Schatz stent is used.
- Follow up on this and the other trials included in the review is for one year or less which is too short a time to properly evaluate the procedures and their associated costs.
- Further trials need to be assessed when they become available in order to establish the costs and benefits for emergency stent insertion and stenting in unfavourable lesion subsets, in particular, for saphenous vein grafts. In addition, long term effects of using coronary artery stents need to be established.

9. Appendices

9.1 Appendix 1. Angina grading

9.1.1 Grading of stable angina of effort by the Canadian Cardiovascular Society[1]

I. Ordinary physical activity does not cause angina: No angina occurs when walking or climbing stairs; angina does occur with strenuous or rapid or prolonged exertion at work or recreation.
II. Slight limitation of ordinary activity: Angina occurs when walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in the cold, in the wind, under emotional stress, or only during the few hours after awakening; walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
III. Marked limitation of ordinary physical activity:. Angina occurs when walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.
IV. Inability to carry on any physical activity without discomfort: Anginal syndrome may be present at rest.

9.1.2 Grading of unstable angina by Braunwald[2]

I. New onset of severe angina or accelerated angina; no rest pain.
II. Angina at rest within past month but not within preceding 48 hours (Angina at rest, subacute).
III. Angina at rest within 48 hours (Angina at rest, acute).

These three grades of severity can be classified further by the clinical circumstances in which unstable angina occurs.

A. Develops in presence of extracardiac condition that intensifies myocardial ischaemia (secondary unstable angina).
B. Develops in absence of extracardiac condition (primary unstable angina).
C. Develops within 2 weeks after acute myocardial angina (postinfarction unstable angina).

9.2 Appendix 2. RCTs of PTCA vs Stents

Study Group Reported by	Nos.	Target Group	Exclusions	Stent	Follow-up Period
BENESTENT SERRUYS 1994[45] MACAYA 1996[46] FOLEY 1996[47] KEANE 1996[75] LEGRAND 1997[24]	516	single or multiple lesion de novo any native <15mm long >3mm diameter stable angina	ostial bifurcation severe vessel tortuosity presence of thrombus	single Palmaz-Schatz by inflating balloon then PTCA balloon	6 months 12 months
STRESS FISCHMAN 1994[48] COHEN 1995[49] SLOTA 1997[50] SAVAGE 1998[51] GEORGE1998[52] KRUMHOLZ 1997[53]	407	single or multiple lesions de novo any native <15mm long >3mm diameter stable and unstable angina	ostial, bifurcation severe vessel tortuosity multiple focal lesions diffuse disease serious disease of left main presence of thrombus MI <7 days	single Palmaz-Schatz by inflating balloon	6 months 12 months
Switzerland EECKHOUT 1996[54]	84	single lesion de novo right native <20mm long >3mm diameter stable and unstable angina	ostial, bifurcation severe vessel tortuosity presence of thrombus	single Wiktor by over the wire balloon then angioplasty balloon	6 months
Italy VERSACI 1997[55]	120	single lesion de novo left anterior descending native <15mm long >3mm diameter stable and unstable angina	ostial, bifurcation major branching of vessel within lesion total occlusion severe tortuosity of proximal LAD MI <1 month	single Palmaz-Schatz by inflating balloon	12 months
BENESTENT-II SERRUYS 1998[28]	823	one or more lesions de novo any native <18mm long >3mm diameter stable or unstable angina	left main, bifurcation, previous graft in target vessel. MI within one week	one or more Palmaz-Schatz by high pressure	12 months

Study Group Reported by	Nos.	Target Group	Exclusions	Stent	Follow-up Period
SICCO SIRNES 1996[56]	117	single or multiple lesions de novo any native >2.5mm diameter total or functional occlusion	lesions with complex anatomy, poor distal runoff, presence of thrombus, major dissection, elastic recoil >50% after balloon inflation, previously dilated segments, previous treatment with other devices, occlusions <2 weeks old.	1 or more Palmaz-Shatz by inflating balloon	6 months
GISSOC RUBARTELLI 1998[57]	110	single lesion any native <13mm long >3mm diameter chronic coronary occlusion	severe tortuosity, bifurcation, difuse disease or complex dissection contraindication to aspirin, warfarin MI within 1 month or chest pain within 7 days	Palmaz-Schatz by inflating balloon	9 months
Britain HANCOCK 1998[58]	60	any native >3mm diameter coronary occlusion for 3 days or more	contraindication to anticoagulation presence of thrombus	Palmaz-Schatz Wiktor or AVE	6 months
GRAMI RODRIGUEZ 1998[60]	104	chest pain >30 mins, ECG changes, onset of symptoms <24 hrs, <75yrs old, cardiogenic shock, vessel >2.5mm diameter	severe left main or multiple vessel disease, stenosis >50% contraindication to heparin or antiplatelets	Gianturco Roubin II	12 months
FRESCO ANTONIUCCI 1998[59]	150	chest pain >30 mins, ECG changes, onset of symptoms <24 hrs, cardiogenic shock, vessel >2.5mm diameter	stenosis <70%of target artery, previous fibrinolytic treatment, non-optimal PTCA	Gianturco Roubin	6 months
Holland SURYA-PRANATA 1998[61]	227	any native artery suitable for stenting, acute MI, onset of symptoms <24 hrs	unprotected left main or severe multivessel disease, bifurcation, diffuse disease, vessel tortuosity, extensive thrombus inability to cross target lesion, no reflow.	Palmaz Schatz	6 months

Study Group Reported by	**Outcome Measures**	**Immediate Clinical Results - for stent group vs PTCA**	**Immediate Angiographic Results - for stent group vs PTCA**
BENESTENT SERRUYS 1994[45] MACAYA 1996[46] FOLEY 1996[47] KEANE 1996[75] LEGRAND 1997[24]	Rate of restenosis = or >50% death, MI, CVA CABG or repeat intervention of same lesion	Increased bleeding and vascular complications (groin hematomas, pseudoaneurysms) Increased length of hospital stay	Increased minimal lumen diameter. Decreased % stenosis
STRESS FISCHMAN 1994[48] COHEN 1995[49] SLOTA 1997[50] SAVAGE 1998[51] GEORGE1998[52] KRUMHOLZ 1997[53]	Rate of restenosis >50% death, MI CABG or repeat intervention of same lesion bleeding and vascular complications	No significant differences	Increased minimal lumen diameter. Decreased % stenosis
Switzerland EECKHOUT 1996[54]	Rate of restenosis = or >50% early vessel closure death, MI, CVA, angina CABG or repeat intervention vascular complications at puncture site duration of hospital stay	Increased vascular complications Increased length of hospital stay	Increased minimal lumen diameter Decreased % stenosis
Italy VERSACI 1997[55]	Rate of restenosis >50% death, MI event free survival CABG or repeat intervention vascular and bleeding complications at puncture site	Increased vascular complications Increased length of hospital stay	Increased minimal lumen diameter Decreased % stenosis
BENESTENT-II SERRUYS 1998[28]	Rate of restenosis >50% death, MI CABG or repeat PTCA of target vessel, anginal class, cost effectiveness.	No significant differences	Increased minimal lumen diameter Decreased % stenosis

Study Group Reported by	Outcome Measures	Immediate Clinical Results - for stent group vs PTCA	Immediate Angiographic Results - for stent group vs PTCA
SICCO SIRNES 1996[56]	Rate of restenosis = or >50% death, MI, CVA, angina CABG or repeat intervention vascular and bleeding complications duration of hospital stay	Increased bleeding at puncture site Increased length of hospital stay	Increased minimal lumen diameter Decreased % stenosis
GISSOC RUBARTELLI 1998[57]	Rate of restenosis = or >50% minimal lumen diameter at follow up, death, MI, CABG, repeat PTCA, symptomatic status, haemorrhagic events.	(combined with long term in text)	Increased minimal lumen diameter Decreased % stenosis
Britain HANCOCK 1998[58]	Minimal lumen diameter at follow up, reocclusion combined event of death, MI, CABG, repeat PTCA.	No significant differences	Increased minimal lumen diameter Decreased % stenosis
GRAMI RODRIGUEZ 1998[60]	Angiographic restenosis, procedural success, death, repeat MI, recurrent ischaemia, CABG, target vessel revascularization, TIMI flow, event free survival.	Increased TIMI flow Increased event free survival Decreased recurrent ischaemia	Decreased % stenosis
FRESCO ANTONIUCCI 1998[59]	Angiographic evidence of >50% stenosis of target vessel death, repeat MI, recurrent ischaemia, repeat target vessel revascularisation	Decreased recurrent ischaemia Decreased repeat PTCA	Increased minimal lumen diameter Decreased restenosis
Holland SURYA-PRANATA 1998[61]	Death, repeat MI, CABG, repeat PTCA of target vessel.	No significant differences	Increased minimal lumen diameter Decreased % stenosis

Study Group Reported by	Long term Clinical Results - for stent group vs PTCA	Long term Angiographic Results - for stent group vs PTCA	comments
BENESTENT SERRUYS 1994[45] MACAYA 1996[46] FOLEY 1996[47] KEANE 1996[75] LEGRAND 1997[24]	Increased event free survival at 12 months. Decreased risk PTCA 7 months + 12 months Decreased risk any event 7 months + 12 months	Increased reference diameter. Decreased restenosis rate and % stenosis at 7 months.	Largest trial, clearest report.
STRESS FISCHMAN 1994[48] COHEN 1995[49] SLOTA 1997[50] SAVAGE 1998[51] GEORGE1998[52] KRUMHOLZ 1997[53]	No significant differences	Increased minimal lumen diameter. Decreased restenosis rate and %stenosis at 7 months	Target vessel revascularization result p=0.06 taken to be statistically significant by authors of trial report but not in this review
Switzerland EECKHOUT 1996[54]	No significant differences	No significant difference on restenosis rate, %stenosis and minimal lumen diameter	Different stent which is more radio-opaque so borderline restenosis more difficult to judge
Italy VERSACI 1997[55]	Increased event free survival at 12 months	Increased minimal lumen diameter Decreased restenosis rate and % stenosis at 12months.	Some clinical results have to be inferred from text as presentation of results not very clear
BENESTENT-II SERRUYS 1998[28]	Increased event free survival Decreased repeat PTCA	Increased minimal lumen diameter Decreased % stenosis	Includes a, cost effectiveness data which concludes that stents more effective and more costly, b, subgroup follow up angiographically and clinically or clinically only, concludes clinical follow up only increased repeat PTCA rate.

Study Group Reported by	Long term Clinical Results - for stent group vs PTCA	Long term Angiographic Results - for stent group vs PTCA	comments
SICCO SIRNES 1996[56]	Increased angina free survival at 6 months	Increased minimal lumen diameter. Decreased restenosis rate and % stenosis at 6 months.	Some clinical results have to be inferred from text as presentation of results not very clear
GISSOC RUBARTELLI 1998[57]	Increased length of hospital stay Decreased target vessel revascularisation Decreased recurrent ischaemia	Increased minimal lumen diameter. Decreased restenosis rate, reocclusion rate and % stenosis at 9 months.	Does not state how occlusions were found to be for >30 days duration.
Britain HANCOCK 1998[58]	No significant differences	Increased minimal lumen diameter. Decreased reocclusion rate.	Confusing, vaguely written, some clinical results have to be inferred from text as presentation of results not very clear.
GRAMI RODRIGUEZ 1998[60]	Increased event free survival	Not given	Angiographic restenosis rates at follow up not reported
FRESCO ANTONIUCCI 1998[59]	Decreased repeat PTCA Decreased recurrent ischaemia	Increased minimal lumen diameter. Decreased restenosis rate.	Also includes results for nonrandomised comparison group who had non-optimal PTCA result.
Holland SURYA-PRANATA 1998[61]	Increased event free survival Decreased recurrent MI Decreased repeat PTCA.	Not given	Anticoagulation therapy changed during trial from Warfarin to Ticlopidine

9.3 Appendix 3 EuroQol EQ-5D

EQ-5D is a measure of health status developed for use in evaluating health and healthcare. It produces a numeric score for health status on which full health has a value of 1 and death has a value of 0. EQ-5D was developed by an international research group (see EuroQol Group below).

EQ-5D describes health status in terms of 5 dimensions
- Mobility
- Self care
- Usual activity
- Pain/discomfort
- Anxiety/depression

Each dimension is divided into 3 levels
- 1 – no problem
- 2 – some problem
- 3 – extreme problem

By combining different levels from each dimension, EQ-5D defines a total of 243 health states.

In the UK, the relative importance of each level/dimension is known from the results of a national survey of the general population commissioned by the Department of Health in 1993.

How is EQ-5D data collected?

A short 3-page questionnaire is completed by patients themselves. The questionnaire takes about a minute to fill in. The questionnaire records
(a) the level of problems (if any) on each of the 5 dimensions
(b) the patient's rating of their overall health status using a 'thermometer'-like scale, marked 0 – 100
(c) minimal background information on the patient (this can be omitted if it duplicates pre-existing information)

What kind of information does EQ-5D produce?

EQ-5D generates 3 types of data for each patient
(a) a profile, indicating the extent of problems across the 5 dimensions
(b) a weighted health index, based on population values obtained from the 1993 survey

(c) a score on the self-rated 'thermometer', indicating the patient's own assessment of their health state
Examples of the type of information produced from EQ-5D are given in the User Guide.

Age/sex norms have been established for the general population in national surveys conducted in 1993 and replicated in 1995/96. Comparative data are available from a range of clinical studies conducted in the UK and internationally.

What is EQ-5D being used for?

- As an integral part of clinical practice, in monitoring health status of individual patients.
- In the evaluation and audit of health care, by measuring changes in health status in individual patients, and in groups of patients.
- Establishing levels of population health status both locally and nationally.
- Comparison of health status in local communities and practice catchment areas, with national patterns.

In the UK, a NHS Task Group has been set up to co-ordinate the testing of EQ-5D as an outcome measure for use by clinicians and managers.

How is EQ-5D obtained?

EQ-5D is in the public domain, and save for commercial users, there is no fee for its use. Within the UK, advice and support on the use of EQ-5D can be obtained from several sources, including the Centre for Health Economics, University of York (see contact details below). Copies of the EQ-5D questionnaire can be obtained from the Centre, together with an abbreviated User Guide. Both are supplied free on request. International enquiries may also be directed to the EuroQol Group's administrative office in Rotterdam, who can also supply copies of a more comprehensive User Guide.

What is the EuroQol Group?

Set up in 1987, the EuroQol Group is an international network of researchers from different disciplines, including medicine, psychology and economics. Membership of the Group is open to those who contribute to the further development of EQ-5D, and to investigators with direct experience of its use. A small administrative office in Rotterdam provides support for the network, and co-ordinates links with external agencies. EQ-5D is in use in most countries around the world, and has been translated into all major languages. The Group oversees that translation process.

How is the EuroQol Group funded?

Individual researchers contribute a nominal sum for annual membership. Where commercial interests are involved, a user fee may apply. Contact the Rotterdam office for details. Bids for European funding have been submitted. Individual members of the EuroQol Group are free to act as consultants in advising on the use of EQ-5D, but may charge accordingly for their services.

For further details contact

Paul Kind
Centre for Health Economics
University of York
York YO1 5DD
England
Tel: 01904 433 653
FAX: 01904 433 644
e-mail: pk1@york.ac.uk

Frank de Charro
Centre for Health Policy and Law
Erasmus University
PO Box 1738, 3000 DR Rotterdam
Netherlands
Tel: + 31 10 408 1545
FAX: + 31 10 452 5303
e-mail: deCharro@gbr.frg.eur.nl

9.3.1 Euroqol questionnaire

Your own health state today

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

1. Mobility

I have no problems in walking about
I have some problems in walking about
I am confined to bed

2. Self-Care

I have no problems with self-care
I have some problems washing or dressing myself
I am unable to wash or dress myself

3. Usual Activities (eg. Work, study, housework, family or leisure activities)

I have no problem with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

4. Pain/Discomfort

I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

5. Anxiety/Depression

I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed

Estimated weights for EQ-5D health states

1 1 1 1 1	1.000	1 2 3 3 2	-0.005	2 1 3 2 3	0.128
1 1 1 1 2	0.848	1 2 3 3 3	-0.170	2 1 3 3 1	0.101
1 1 1 1 3	0.414	1 3 1 1 1	0.436	2 1 3 3 2	0.030
1 1 1 2 1	0.796	1 3 1 1 2	0.365	2 1 3 3 3	-0.135
1 1 1 2 2	0.725	1 3 1 1 3	0.200	2 2 1 1 1	0.746
1 1 1 2 3	0.291	1 3 1 2 1	0.313	2 2 1 1 2	0.675
1 1 1 3 1	0.264	1 3 1 2 2	0.242	2 2 1 1 3	0.241
1 1 1 3 2	0.193	1 3 1 2 3	0.077	2 2 1 2 1	0.623
1 1 1 3 3	0.028	1 3 1 3 1	0.050	2 2 1 2 2	0.552
1 1 2 1 1	0.883	1 3 1 3 2	-0.021	2 2 1 2 3	0.118
1 1 2 1 2	0.812	1 3 1 3 3	-0.186	2 2 1 3 1	0.091
1 1 2 1 3	0.378	1 3 2 1 1	0.400	2 2 1 3 2	0.020
1 1 2 2 1	0.760	1 3 2 1 2	0.329	2 2 1 3 3	-0.145
1 1 2 2 2	0.689	1 3 2 1 3	0.164	2 2 2 1 1	0.710
1 1 2 2 3	0.255	1 3 2 2 1	0.277	2 2 2 1 2	0.639
1 1 2 3 1	0.228	1 3 2 2 2	0.206	2 2 2 1 3	0.205
1 1 2 3 2	0.157	1 3 2 2 3	0.041	2 2 2 2 1	0.587
1 1 2 3 3	-0.008	1 3 2 3 1	0.014	2 2 2 2 2	0.516
1 1 3 1 1	0.556	1 3 2 3 2	-0.057	2 2 2 2 3	0.082
1 1 3 1 2	0.485	1 3 2 3 3	-0.222	2 2 2 3 1	0.055
1 1 3 1 3	0.320	1 3 3 1 1	0.342	2 2 2 3 2	-0.016
1 1 3 2 1	0.433	1 3 3 1 2	0.271	2 2 2 3 3	-0.181
1 1 3 2 2	0.362	1 3 3 1 3	0.106	2 2 3 1 1	0.383
1 1 3 2 3	0.197	1 3 3 2 1	0.219	2 2 3 1 2	0.312
1 1 3 3 1	0.170	1 3 3 2 2	0.148	2 2 3 1 3	0.147
1 1 3 3 2	0.099	1 3 3 2 3	-0.017	2 2 3 2 1	0.260
1 1 3 3 3	-0.066	1 3 3 3 1	-0.044	2 2 3 2 2	0.189
1 2 1 1 1	0.815	1 3 3 3 2	-0.115	2 2 3 2 3	0.024
1 2 1 1 2	0.744	1 3 3 3 3	-0.280	2 2 3 3 1	-0.003
1 2 1 1 3	0.310	2 1 1 1 1	0.850	2 2 3 3 2	-0.074
1 2 1 2 1	0.692	2 1 1 1 2	0.779	2 2 3 3 3	-0.239
1 2 1 2 2	0.621	2 1 1 1 3	0.345	2 3 1 1 1	0.367
1 2 1 2 3	0.187	2 1 1 2 1	0.727	2 3 1 1 2	0.296
1 2 1 3 1	0.160	2 1 1 2 2	0.656	2 3 1 1 3	0.131
1 2 1 3 2	0.089	2 1 1 2 3	0.222	2 3 1 2 1	0.244
1 2 1 3 3	-0.076	2 1 1 3 1	0.195	2 3 1 2 2	0.173
1 2 2 1 1	0.779	2 1 1 3 2	0.124	2 3 1 2 3	0.008
1 2 2 1 2	0.708	2 1 1 3 3	-0.041	2 3 1 3 1	-0.019
1 2 2 1 3	0.274	2 1 2 1 1	0.814	2 3 1 3 2	-0.090
1 2 2 2 1	0.656	2 1 2 1 2	0.743	2 3 1 3 3	-0.255
1 2 2 2 2	0.585	2 1 2 1 3	0.309	2 3 2 1 1	0.331
1 2 2 2 3	0.151	2 1 2 2 1	0.691	2 3 2 1 2	0.260
1 2 2 3 1	0.124	2 1 2 2 2	0.620	2 3 2 1 3	0.095
1 2 2 3 2	0.053	2 1 2 2 3	0.186	2 3 2 2 1	0.208
1 2 2 3 3	-0.112	2 1 2 3 1	0.159	2 3 2 2 2	0.137
1 2 3 1 1	0.452	2 1 2 3 2	0.088	2 3 2 2 3	-0.028
1 2 3 1 2	0.381	2 1 2 3 3	-0.077	2 3 2 3 1	-0.055
1 2 3 1 3	0.216	2 1 3 1 1	0.487	2 3 2 3 2	-0.126
1 2 3 2 1	0.329	2 1 3 1 2	0.416	2 3 2 3 3	-0.291
1 2 3 2 2	0.258	2 1 3 1 3	0.251	2 3 3 1 1	0.273
1 2 3 2 3	0.093	2 1 3 2 1	0.364	2 3 3 1 2	0.202
1 2 3 3 1	0.066	2 1 3 2 2	0.293	2 3 3 1 3	0.037

2 3 3 2 1	0.150	3 1 3 3 3	-0.380	3 3 1 2 2	-0.072
2 3 3 2 2	0.079	3 2 1 1 1	0.232	3 3 1 2 3	-0.237
2 3 3 2 3	-0.086	3 2 1 1 2	0.161	3 3 1 3 1	-0.264
2 3 3 3 1	-0.113	3 2 1 1 3	-0.004	3 3 1 3 2	-0.335
2 3 3 3 2	-0.184	3 2 1 2 1	0.109	3 3 1 3 3	-0.500
2 3 3 3 3	-0.349	3 2 1 2 2	0.038	3 3 2 1 1	0.086
3 1 1 1 1	0.336	3 2 1 2 3	-0.127	3 3 2 1 2	0.015
3 1 1 1 2	0.265	3 2 1 3 1	-0.154	3 3 2 1 3	-0.150
3 1 1 1 3	0.100	3 2 1 3 2	-0.225	3 3 2 2 1	-0.037
3 1 1 2 1	0.213	3 2 1 3 3	-0.390	3 3 2 2 2	-0.108
3 1 1 2 2	0.142	3 2 2 1 1	0.196	3 3 2 2 3	-0.273
3 1 1 2 3	-0.023	3 2 2 1 2	0.125	3 3 2 3 1	-0.300
3 1 1 3 1	-0.050	3 2 2 1 3	-0.040	3 3 2 3 2	-0.371
3 1 1 3 2	-0.121	3 2 2 2 1	0.073	3 3 2 3 3	-0.536
3 1 1 3 3	-0.286	3 2 2 2 2	0.002	3 3 3 1 1	0.028
3 1 2 1 1	0.300	3 2 2 2 3	-0.163	3 3 3 1 2	-0.043
3 1 2 1 2	0.229	3 2 2 3 1	-0.190	3 3 3 1 3	-0.208
3 1 2 1 3	0.064	3 2 2 3 2	-0.261	3 3 3 2 1	-0.095
3 1 2 2 1	0.177	3 2 2 3 3	-0.426	3 3 3 2 2	-0.166
3 1 2 2 2	0.106	3 2 3 1 1	0.138	3 3 3 2 3	-0.331
3 1 2 2 3	-0.059	3 2 3 1 2	0.067	3 3 3 3 1	-0.358
3 1 2 3 1	-0.086	3 2 3 1 3	-0.098	3 3 3 3 2	-0.429
3 1 2 3 2	-0.157	3 2 3 2 1	0.015	3 3 3 3 3	-0.594
3 1 2 3 3	-0.322	3 2 3 2 2	-0.056		
3 1 3 1 1	0.242	3 2 3 2 3	-0.221		
3 1 3 1 2	0.171	3 2 3 3 1	-0.248		
3 1 3 1 3	0.006	3 2 3 3 2	-0.319		
3 1 3 2 1	0.119	3 2 3 3 3	-0.484		
3 1 3 2 2	0.048	3 3 1 1 1	0.122		
3 1 3 2 3	-0.117	3 3 1 1 2	0.051		
3 1 3 3 1	-0.144	3 3 1 1 3	-0.114		
3 1 3 3 2	-0.215	3 3 1 2 1	-0.001		

Unconscious (-0.402)
Note: this value is the mean observed score. It does not result from the regression model.

Source: A1 TARIFF BASED ON UK SURVEY(1993)

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