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Review

Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness

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Health Technology Assessment
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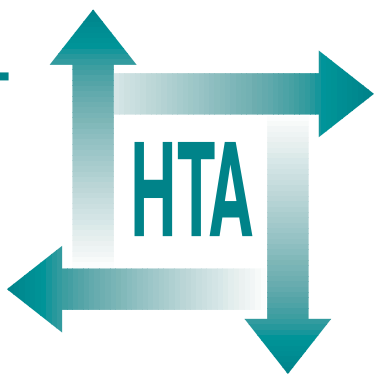

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Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness

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NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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

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Contents

List of abbreviations i

Executive summary iii

1 Background 1
Coronary artery disease: an overview 1
Interventional cardiology 3
Intracoronary ultrasound – potential applications in interventional cardiology 5
The technical development of IVUS 6
Decision-analytic modelling 8
Conclusion 8

2 Research questions 9

3 Review methods 11
Literature review 11
Data synthesis 16
Decision-analytic model 16
Conclusion 20

4 Studies included in the review 23
Detailed analysis of search methodology 23
Articles included in the review 30
Decision-analytic model 46
Conclusion 56

5 Studies excluded from the review 57
IVUS-guided interventions 57
Control arm 57
Additional topics 57
Economics 57

6 Results of the review 61
IVUS-guided primary stenting 61
IVUS-guided optimisation of PTCA 66
Other IVUS-guided coronary interventions 66
IVUS-guided therapy for in-stent restenosis 66
What are the *in-vivo* intra- and inter-observer reproducibilities of measurements made using IVUS? 66

7 Sensitivity analysis 67
Methods 67
Results 68
Conclusions 72

8 Discussion 73
Methodology 73
Results of the review 77
Changes in the knowledge base 79

9 Conclusions 81
Implications for healthcare 81
Recommendations for further research 81

Acknowledgements 83

References 85

Appendix 1 Definitions 99

Appendix 2 Search strategies 101

Appendix 3 The systematic search of the Internet 105

Appendix 4 Checklists: IVUS-guided interventions 107

Health Technology Assessment reports published to date 109

Health Technology Assessment Programme 115

List of abbreviations

ACS	acute coronary syndromes
AHA	American Heart Association*
AMI	acute myocardial infarction
AVID	Angiography Versus Intravascular ultrasound Directed coronary stent placement [study]
BIDS	Bath Information & Data Services
CABG	coronary artery bypass graft
CCS	Canadian Cardiovascular Society
CI	confidence interval
CRUISE	Can Routine Ultrasound Influence Stent Employment [study]
CSA	cross-sectional area
CT	computed tomography
CVA	cardiovascular accident*
DARE	Database of Reviews of Effectiveness
DCA	directional coronary atherectomy
DEC	Development and Evaluation Committee
ELCA	excimer laser coronary atherectomy
EEM	external elastic membrane
ICER	incremental cost-effectiveness ratio
ICUS	intracoronary ultrasound
IDDM	insulin-dependent diabetes mellitus
ISTP	Index of Scientific and Technical Proceedings*
ITT	intention-to-treat
IVUS	intravascular ultrasound
LAD	left anterior descending [coronary artery]
LCx	left circumflex coronary artery*
LM	left main coronary artery*
LMWH	low molecular weight heparin
LVEF	left ventricular ejection fraction*
MACE	major adverse cardiac event
MeSH	medical subject heading
MI	myocardial infarction
MLD	minimal lumen diameter
MRI	magnetic resonance imaging
MUSIC	Multicenter Ultrasound Stenting in Coronaries [study]
NIDDM	non-insulin dependent diabetes mellitus
OPTICUS	Optimization with ICUS to reduce stent restenosis [study]
POBA	"plain old balloon angiography"
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality-adjusted life year
QCA	quantitative coronary angiography
RCT	randomised controlled trial
ROTA	rotational atherectomy
RR	relative risk*
SCI	Science Citation Index*
SD	standard deviation
SE	standard error
SIPS	Strategy of ICUS-guided PTCA and Stenting [study]
STARS	Stent Anti-thrombotic Regimen Study
STRESS	Stent Restenosis Study
TEC	transluminal extraction catheter
TLR	target lesion revascularisation
WEST	West European Stent Trial
WWW	World Wide Web

* Used only in tables and figures

Executive summary

Background

Intravascular ultrasound (IVUS) is the generic name for any ultrasound technology used *in vivo* within the blood vessels. More specifically, intracoronary ultrasound enables imaging of the coronary arteries from within the lumen. This review concentrates on the role of intracoronary ultrasound as an adjunct to interventional cardiology.

Objectives

- To identify the literature on IVUS for guiding coronary interventions, and to synthesise evidence about outcomes compared with outcomes when IVUS guidance has not been used.
- To use this evidence, together with other information about costs and outcomes, to model the cost effectiveness of IVUS guidance.
- To synthesise the evidence on the reproducibility of measurements of cross-sectional area made using IVUS.

Methods

Data sources

- Electronic searches of MEDLINE, EMBASE, Science Citation Index, Index to Scientific and Technical Proceedings, Engineering Compendex, Engineering Page One, Cochrane Library, Inside (British Library), 1990–98.
- Contacting experts and centres of expertise, 1990–99.
- Internet search, 1990–99.

Study selection

Studies of IVUS-guided coronary interventions performed on humans were included in the review. Non-English language studies were also included when they covered IVUS-guided stenting or angioplasty. Control evidence regarding outcomes without IVUS guidance was sought only from randomised controlled trials (RCTs). Studies investigating the reproducibility of measurements of cross-sectional area were included only if the results were expressed in terms of the mean and standard deviation of paired differences.

Data extraction

Checklists that covered study details, patient characteristics and results were completed independently by three reviewers. Consensus was reached on any disagreements. Local data were gathered on the costs of IVUS-guided stenting.

Data synthesis

Overall event rates were calculated by pooling patient results from the included studies. A decision-analytic model was used to combine information from the literature with cost estimates, in order to predict cost-effectiveness in terms of cost per restenosis event avoided by the use of IVUS guidance. The analysis was performed from the perspective of the healthcare provider. Sensitivity analysis was undertaken. A simple extrapolation was made to long-term outcome so that cost–utility (using quality-adjusted life years (QALYs)) could be estimated. The minimum detectable change in cross-sectional area was estimated from the reproducibility results.

Results

Only one study on IVUS-guided angioplasty satisfied the inclusion criteria, and there were no studies on IVUS-guided atherectomy or other IVUS-guided interventions that satisfied the inclusion criteria. Of the 15 articles on IVUS-guided stenting that satisfied the inclusion criteria, seven presented data on outcomes at 6 months post-intervention. The angiographic restenosis rate was 16 ± 1%. This compared with 24 ± 2% derived from five articles on stenting without IVUS guidance. Data for follow-up periods longer than 6 months were presented in only two studies.

Data from a total of five studies were included in the decision-analytic model. The cost per restenosis event avoided was £1545. After extrapolation to long-term outcome, the calculated cost per QALY was £6438. The baseline QALY gain was only 0.03 years. Sensitivity analysis resulted in large differences between the best- and worst-case scenarios, for example, from a saving of £5000 to a cost of £24,000 per restenosis event avoided.

The smallest changes in cross-sectional area that could be measured were 1.6 mm^2 by a single observer and 1.9 mm^2 by different observers.

Conclusions

Implications for healthcare

- The evidence available is too weak for there to be any reliable implications for clinical practice.

Recommendations for research

- An adequately powered, well-designed RCT comparing the long-term outcomes of stenting, with and without IVUS guidance.
- An RCT to compare acute and subacute thrombosis rates and long-term outcome of high pressure stent implantation strategies with and without IVUS guidance.
- An RCT to compare the long-term outcome of therapy guided by IVUS against the 'intention-to-stent' approach using angiographic guidance.
- Studies of cost and cost-effectiveness based on the results of these RCTs, which follow guidelines for the measurement and valuation of costs.
- There is a strong case for a prospective audit of all stenting procedures carried out in the UK to commence as soon as possible, along clearly defined lines that address the gaps in currently available data.
- Updating of the decision model presented here when results are available from trials currently underway.
- Monitoring of expert opinion (horizon scanning) to identify future roles for IVUS, and early implementation of adequately powered RCTs to test emergent applications.
- Measures to facilitate modelling should include the development of guidelines to authors about the style of data presentation necessary, support for supplementary data to be held on web servers, and routine collection of registry and local data.
- A structured review of the therapeutic and outcome impact of using IVUS to detect calcification and eccentric lesions.

Chapter 1
Background

Intravascular ultrasound (IVUS) is the generic name for any ultrasound technology that is used *in vivo* within blood vessels. More specifically, intracoronary ultrasound (ICUS) provides the ability to image the coronary arteries from within the lumen and is the focus of this review. ICUS has evolved into an adjunct to interventional cardiology and it is this role that is concentrated on in this review.

In this chapter introductory information is presented that both describes the technology and places it in its clinical context, especially in relation to interventional cardiology. Descriptions are provided of coronary artery disease and its manifestations, its incidence and prevalence and the available management options. Terms that will be used extensively in later chapters are defined and attention is drawn to those areas in which IVUS may have a role. This is followed by an overview of the technical development of the technology, from which it is apparent that IVUS is an 'evolving' technology.[1,2]

The hierarchical structure proposed by Fineberg[3] and others[4,5] is valuable when considering the effectiveness of diagnostic devices. The levels of the hierarchy are technical performance, diagnostic performance, diagnostic impact, therapeutic impact, patient outcome and health economic impacts. The most appropriate study design to investigate performance at each level was outlined in an earlier review.[6] By considering the levels separately it is much easier to classify articles and discuss their findings. In terms of dissemination, the results of a review can be made more accessible to different healthcare professionals and consumers, who seek evidence of effectiveness at different levels of the hierarchy. The hierarchy is applicable even when an imaging device is being used for purposes other than diagnosis, as in the case here in which the focus is on its use for guidance of interventional procedures, because the higher levels may be considered independently from the lower ones. The review concentrates on the levels of patient outcome and health economics.

In most fields where the health technology is under rapid development, there is a lack of evidence about the impact of the technology on both outcome for the patient and economic issues. This may be because insufficient time has passed for conclusions to be drawn or because large, reliable studies cannot be performed as the technology is continually improving. In such situations, the technique of decision-analytic modelling is increasingly used as an adjunct to the conventional systematic literature review.[7] Modelling forms a large part of this review and this chapter closes with an overview of the technique.

Coronary artery disease: an overview

With each heartbeat the heart ejects blood from the left ventricle through the aortic valve into the aorta, which then, through a series of branches, carries blood to the rest of the body. The coronary arteries are the blood vessels that carry oxygenated blood to the myocardium (the muscle of the heart) and they arise from the aorta just above the aortic valve. There are usually two, the left and the right. The left divides into two branches, the left anterior descending (LAD) and the circumflex, and these further subdivide into a series of branches that supply predominantly the left ventricle. The initial part of the left coronary artery before it divides is known as the left main stem. The right coronary artery via its branches supplies the right ventricle and a variable amount of the inferior surface of the left ventricle.

Coronary artery disease is the development of narrowings (stenoses) in the walls of the coronary arteries caused by plaques of atheroma that, in time, lead to partial or complete obstruction of normal blood flow and the development of myocardial ischaemia. Atheroma of the coronary arteries presents in a variety of ways, including stable or unstable angina, acute myocardial infarction (AMI) or sudden death. The events described by the acronym MACE (major adverse cardiac event) are: death, Q-wave myocardial infarction (MI), non-Q-wave MI and revascularisation. The pain of myocardial ischaemia is characterised by a heavy, pressing chest pain that typically radiates to the jaw or left arm. In stable angina the pain is precipitated by exertion and

relieved by rest, whereas in unstable angina and MI the pain occurs at rest. The difference between unstable angina and MI is the presence of myocardial cell death or necrosis with infarction. In recent years it has become increasingly clear that these are different expressions of the same underlying pathophysiological process, namely plaque rupture and partial or total coronary occlusion which may be transient or permanent, and that they form part of a continuum with substantial overlap between them.

Epidemiology

Estimates of the prevalence and incidence of coronary artery disease vary widely depending, in part, on the definition of the disease and the population under study. For example, taking angina as the index for coronary atheroma will exclude those patients who present with MI as well as those with symptomatically silent disease. Nonetheless, as symptomatic angina is the main reason for invasive investigation and management (angioplasty and surgery) of patients with coronary artery disease, the incidence and prevalence of angina gives an indication of the demand for these treatments. In population studies in the UK the prevalence of angina is about 2%.[8,9] In men aged 40–60 years, prevalence is between 5% and 10%.[10,11] The incidence (new cases per population per year) ranges from 0.44/1000 per year (men aged 31–40 years) to 2.32/1000 per year (men aged 61–70 years) and from 0.08/1000 to 1.01/1000 per year, respectively, in women. This gives a figure for the UK of about 22,000 new cases per year.[12] However, the total burden of coronary disease is higher than this as many patients will present with infarction rather than angina. Only about one in five patients with infarction have a prior history of angina.[13]

Pathophysiology

The fundamental processes underlying coronary atheroma are endothelial damage, lipid accumulation and smooth muscle cell proliferation. As the atheromatous plaque enlarges, the vessel lumen blood flow is restricted. A stenosis of more than 50% is of haemodynamic significance, with compromise to coronary flow with effort. As myocardial work increases, for example, with exercise, myocardial oxygen demand increases. This is normally accommodated by an increase in coronary blood flow. If demand exceeds supply, the myocardium becomes ischaemic and angina is the symptomatic expression of this. Not all ischaemia causes angina. The threshold at which ischaemia causes pain varies between patients and most have episodes of silent ischaemia that are unaccompanied by pain. In some patients all ischaemic episodes may be silent. The acute coronary syndromes (unstable angina and MI) occur when coronary plaques rupture. Here the lining of the coronary artery overlying the plaque (the endothelium) tears and exposes the core of the plaque to flowing blood. The plaque core contains a variety of highly thrombogenic substances and, through the processes of platelet aggregation and fibrin formation, the lumen becomes acutely narrowed or occluded. This causes a sudden severe reduction in blood flow with resultant myocardial ischaemia at rest presenting as unstable angina. If the vessel becomes occluded and this is sustained, myocardial tissue dies. This is MI.

The precise process of atherogenesis is poorly understood but a variety of factors are associated with an increased risk of developing coronary artery disease.[14,15] The best characterised of these are smoking, diabetes mellitus, hypertension, hypercholesterolaemia and a family history of premature coronary artery disease. Patients with one or more of these abnormalities are more likely to develop angina or have heart attacks, and there are now risk functions by which the probability of death or non-fatal MI can be estimated over a 10-year period for patients with various constellations of risk factors.[16]

Management

Stable angina

The initial approach to the management of patients with chronic stable angina is to treat their symptoms and control their risk factors. For example, lipid-lowering therapy has been shown to reduce recurrent events in patients with hypercholesterolaemia.[17] A number of different drug classes have been shown to be effective in controlling symptoms and improving exercise times in patients with symptomatic stable angina.[18] Angina is a manifestation of the same disease process as MI and, hence, it is associated with an increased risk of infarction and death. This process is in part driven by platelet aggregation in response to plaque rupture, and anti-platelet drugs such as aspirin reduce the risk of MI and death in patients with angina.[19]

In those whose symptoms are not controlled by medical therapy, two other treatment options exist. Taken in chronological order, the first is the surgical procedure of coronary artery bypass

grafting (CABG). This was first undertaken in 1964 in Houston, Texas, as a bail-out procedure during another cardiac surgical procedure,[20] although the first series was performed in Cleveland, Ohio, starting in May 1967 and reported in 1968.[21] The procedure involves taking segments of vein, usually from the leg, connecting them to the aorta and then to the coronary artery distal to the stenoses. This allows normal blood flow to be restored to that portion of myocardium. Depending on the coronary anatomy, as many as five grafts may be necessary, and this has to be assessed by coronary angiography beforehand. Unfortunately, vein grafts do not tolerate arterial blood pressures well and there is an early attrition rate; this approaches 10% by 1 month and about 50% by 5 years, although in one series a third were still patent after 20 years.[22] Consequently, arterial grafts are also used, most commonly the left internal mammary artery which is redirected from its normal course down the back of the sternum (breastbone) to the heart. These grafts have much better long-term survival rates, with 10-year patency rates of over 90%. In appropriately selected patients, surgery is highly effective in treating symptomatic angina.

The alternative strategy to surgical revascularisation is percutaneous transluminal coronary angioplasty (PTCA). This is discussed more fully later as it is an intervention in which IVUS may have an adjunctive role.

Unstable angina

In both unstable angina and MI, the immediate problem is platelet aggregation and intracoronary thrombosis. Again anti-platelet therapy, usually with aspirin, has been shown to reduce the risk of death. In the case of MI with S-T elevation on the ECG, thrombolysis with drugs that lyse fibrin clot reduce mortality when given within 12 hours.[23] The precise role of revascularisation in unstable angina and non-Q wave MI, whether surgical or by angioplasty, remains controversial.[23–25]

Investigations

A number of non-invasive investigations can be used. These include exercise testing, stress imaging with radionuclide techniques or echocardiography, X-ray angiography, X-ray computed tomography (CT) and magnetic resonance imaging (MRI). IVUS is increasingly being used to complement the information from angiography but this aspect of its use is not be covered in this review.

Interventional cardiology

Development of PTCA

Mason Sones first carried out selective coronary angiography in October 1958. Some 20 years later, in September 1977, Andreas Gruentzig carried out the first PTCA in Zurich, Switzerland. Subsequently, there has been an exponential growth, both in the range of techniques and indications, and in the number of patients experiencing the techniques (over 800,000 worldwide in 1995).[22] The concept of PTCA is fundamentally simple. The coronary artery is selectively engaged with a guide catheter (a 1 metre length of tubing with a diameter slightly over 2 mm), which has been introduced into the arterial circulation via either the femoral, radial or brachial artery. A guide wire (0.014 inches or 0.36 mm in diameter) is passed up the catheter to the coronary artery and steered into the artery and across the stenosis. A balloon catheter (a smaller tube with a deflated balloon of about 2 cm length and a diameter, when inflated, of between 1.5 and 4 mm near its tip) is then passed over the wire so that it follows into the narrowing. The balloon is inflated to somewhere between 4 and 16 atmospheres. The physical properties of the balloon material ensure that when inflated it does not expand much beyond its nominal diameter, a 3 mm balloon achieves a diameter of 3 mm at 8 atmospheres and, perhaps, 3.3 mm at 16 atmospheres. The aim is for the stenosis to have been reduced following dilatation and to be no longer haemodynamically significant.

As originally conceived by Gruentzig, PTCA was applied to patients with limiting chronic stable angina and discrete stenoses in a single coronary artery. In subsequent years, the complexity and number of lesions and vessels subjected to angioplasty have expanded. Interventions are now undertaken in vein grafts and multivessel disease, and in patients with acute coronary syndrome (ACS) and even left main stem disease. This diversification has been possible because of the dramatic improvements in the technology of interventional cardiology, with improved guide catheters and balloons, steerable guidewires and additional devices, such as stents and digital imaging systems. In contrast, when Gruentzig started he did not, for example, have guidewires and had to directly steer the large stiff balloon catheter into the artery without one.

For the first patients who underwent PTCA under Gruentzig, the results were dramatic. The patients were highly symptomatic, usually young and with discrete single vessel disease, and their

only alternative was CABG. After PTCA they were asymptomatic and their stress test returned to normal. Greuntzig's first patient underwent repeat angiography after 10 years and the vessel had remained widely patent. In 1997 this patient completed a maximal exercise stress test and he remains asymptomatic. Gruentzig treated 169 patients before he left Zurich in 1980. The 10-year survival for this group was 90% and for those with single vessel disease it was 95%. CABG was necessary in 23% over the 10 years.[26,27]

Problems with PTCA

As experience grew, it became apparent that there were problems associated with PTCA. IVUS has the potential to help address some of these.

Acute closure

In the first 3500 patients treated at Emory University Hospital, Atlanta, Georgia, the most feared complication, occurring in about 4.4% of cases, was acute closure of the vessel especially if it necessitated urgent surgery in a haemodynamically unstable patient.[28] Acute closure results from dissection of the vessel. A tear within the layers of the vessel wall causes a flap of endothelium to obstruct the lumen.

Recoil

A vessel responds to balloon inflation by dilating and the balloon is seen to expand but within a few minutes of deflation the vessel recoils and the target lesion is still significant.

Restenosis

A significant proportion of patients develop restenosis in the longer term. The lesion that was originally dilated successfully recurs and the patient re-presents with recurrent symptoms. Restenosis rates of anything between 12% and 53% have been reported and a number of correlates of restenosis identified, including lesion site, vessel size, lesion severity and residual stenosis after PTCA. Despite extensive efforts to identify agents that would modify this process none were found.[29]

Failed PTCA

In addition to the catastrophe of acute closure, PTCA may fail because the lesion cannot be dilated, the wire or balloon will not cross the lesion site, the lesion recoils after the balloon is deflated, or the residual stenosis is still greater than 50%.

Adjuncts to PTCA

It became apparent that lesion characteristics influence the outcome of PTCA. Short discrete concentric lesions are more likely to respond successfully to PTCA than long, eccentric calcified ones for example. A variety of devices have been developed to deal with some of these problems. These often involve some form of 'debulking' in which the burden of atheroma in the vessel is reduced prior to PTCA. The choice of device might be guided by information acquired using IVUS.

Directional atherectomy

The concept underlying directional coronary atherectomy (DCA) is the removal of the atherosclerotic tissue from the vessel wall, rather then the plaque compression or arterial dilatation resulting from PTCA.

Transluminal extraction catheter

The transluminal extraction catheter (TEC) is designed to remove circumferentially friable or thrombotic material from the vessel and has been used particularly in degenerating vein grafts. It has been reserved for higher risk lesions including acute infarction, for which there does seem to be some benefit.[30]

Rotational atherectomy

Rotational atherectomy (ROTA) uses a device, the Rotablator® (Boston Scientific), that consists of a diamond-coated burr that spins at rates of between 150,000 and 200,000 rpm. It abrades tissue in a similar fashion to a dental drill and tends to selectively ablate firm fibrotic or calcific tissue. It generates particles the size of red blood cells that are taken up by the reticulo-endothelial system. The device has proved invaluable in lesions that cannot be dilated by balloon alone, allowing full expansion and adequate stent deployment in hard calcific lesions.[31,32]

Laser angioplasty

Laser energy is transported down a flexible fibre-optic tube and, on direct contact with tissue, ablates it by vaporisation and shock waves.

Stents

The introduction of intracoronary stents has revolutionised the practice of interventional cardiology. Stents are endoprosthetic scaffolding devices, usually metallic and based on a slotted tube or a coil design. They are deployed on a balloon and inflation of the balloon expands the stent against the wall of the coronary artery, with the exception of self-expanding stents such as the Wall stent. Stents seal dissections, create a rounder, smoother channel within the vessel and enlarge the lumen. In the early days, stents had limited

application because they were unwieldy and not easily deployed into tortuous vessels or complex lesions. However, there has been exponential development in stent design and they now come in a range of diameters and lengths, premounted on dedicated balloons.

Initially, stents were used to treat arteries that had become acutely occluded during PTCA (so-called bail-out stenting). Subsequently, they have been shown to reduce restenosis rates in certain lesion subsets[33,34] – single lesions less than 15 mm in vessels 3–4 mm in diameter – and are now widely used electively for this reason or when the acute result of 'plain old balloon angioplasty' (POBA) is sub-optimal, for example, if there is marked recoil. The major initial problems with stents were thrombotic occlusion in the days after implantation, and the bleeding complications were those of the intensive anticoagulant regimes. Subsequent developments have led to regimes using more powerful anti-platelet regimes, including ticlopidine.[35] Improved drug regimes led to a marked reduction in the subacute thrombosis rate and inpatient hospitalisation fell from 5 or more days to overnight. Day-case PTCA and stenting is now performed at some centres.

Stenting practice was again modified when IVUS was used to evaluate the success of stent deployment. IVUS demonstrated that many stents were not fully deployed at conventional dilation pressures (6–8 atmospheres). A subsequent high-pressure deployment stategy achieved better acute results,[36] and this has now become standard practice.

While stents reduce the restenosis rate in appropriate lesion subsets, they do not abolish it. Careful quantitative angiographic studies have demonstrated that after stenting a vessel the increase in minimal lumen diameter (MLD) – the 'acute gain' – was greater than after PTCA alone. Subsequent reduction in MLD has been due to new tissue growth (neo-intimal hyperplasia) within the stent. This 'late loss' is paradoxically greater following stenting. However, because of the initial greater acute gain, the overall effect is a reduction in the binary restenosis rate (i.e. the proportion of lesions with an angiographic stenosis greater than 50% at follow-up). Unfortunately, when it does occur, in-stent restenosis is more difficult to treat than restenosis after PTCA alone. There may be another role for IVUS in the assessment of in-stent restenosis to guide treatment selection. This is investigated in the literature review.

Intracoronary ultrasound – potential applications in interventional cardiology

Contrast angiography has been the gold standard in the assessment of coronary artery disease for over three decades. However, angiography only provides a picture of the coronary lumen and gives no insight into the state of the vessel wall. Pathological studies reveal that before atherosclerosis encroaches on the lumen, there is compensatory enlargement of the coronary artery, the Glagov phenomenon.[37] Lumen area is not compromised until plaque area exceeds 40% of the total vessel cross-sectional area. IVUS enabled this phenomenon to be studied *in vivo* and confirmed its existence,[38–40] while also highlighting that, in some cases, vessel size could reduce in the presence of atheroma (reversed Glagov).[41–43] These insights led to the evaluation of IVUS as a tool for the interventionalist. There are a number of areas in which IVUS may provide useful additional information, and which were candidates for inclusion in this systematic review. Unfortunately it was not possible to address them all. In particular, applications that rely on the use of IVUS to characterise the composition of a lesion, or to detect angiographically silent atheroma were not addressed. These omitted topics are discussed in chapter 8.

Adjunct to stent implantation

Theoretically, IVUS guidance can facilitate optimal long-term results from stenting in three ways: first, by ensuring that significant residual stenosis or dissection at the stent margins is dealt with; second, by ensuring that plaque calcification that might limit stent expansion is identified and removed, for example, by ROTA; third, by ensuring that an optimal lumen gain has been achieved in the stented segment. Criteria have been developed that define the achievement of optimal stenting (The 'MUSIC' criteria,[44] see appendix 1). These are based on a comparison of the lumen within the stent with the lumen of proximal and distal reference segments together with the presence of complete stent apposition to the vessel wall and a symmetrical stent expansion index, that is, the ratio of minimal to maximal stent lumen diameter. IVUS is now routinely used in some centres to guide stenting procedures and the evidence on how its use affects long-term outcome and costs is reviewed.

Adjunct to balloon angioplasty

The long-term results of angioplasty for individual lesions are not well predicted by angiography.[45]

When measurements were made using IVUS of residual plaque burden and MLD or cross-sectional area (CSA) after intervention, the results suggested that these parameters were indicative of the restenosis risk.[46,47] This has led to the use of IVUS to 'optimise' balloon angioplasty by the performance of additional procedures if indicated by IVUS measurements. The aim is to improve the long-term outcome and obviate the need for additional costly procedures. The evidence relating to the postulated reduction in restenosis and consequent reductions in cost are reviewed.

Adjunct to directional atherectomy

Given the limitations of angiography, it can be difficult to orientate the atherectomy cutter towards the atheroma, particularly in eccentric lesions. IVUS can make the process easier and allow a more aggressive approach without the fear of damage. Greater plaque removal and a larger final lumen[48] are predicted. Theoretically this should result in a better long-term result, and the evidence for this is reviewed.

In-stent restenosis

In-stent restenosis remains a clinically relevant problem, not the least because it can be more difficult to treat successfully than restenosis after balloon angioplasty. The evidence relating to the use of IVUS in assessing in-stent restenosis and guiding the choice of therapy is reviewed.

In each case, the critical question is whether the theoretical benefits can be translated into better results in clinical practice at a cost that is affordable, and this is the main question addressed.

The technical development of IVUS

Three types of ultrasound transducer have been evaluated for use in intravascular applications. These address the two basic challenges of scanning and focusing in different ways.

Scanning system

In any pulse echo system, it is necessary to move the one-dimensional beam over a two-dimensional section in order to create the imaging plane of choice. This is most commonly done by physical rotation of the transducer using a mechanical motor. Alternatively, the rotation can be applied to a mirror, positioned in the catheter tip, which then causes the beam from a stationary transducer to be scanned. The motor can be positioned outside of the patient and connected to the transducer at the catheter tip by means of a Bowden type of cable or else, if suitable miniaturisation is achieved, be contained within the body of the catheter. With advances in technology, more recent devices have generally exploited the latter approach.

Focusing mechanism

Without beam focusing, the divergence of the beam would cause the lateral resolution, and hence the image quality, to be extensively degraded. Focusing can be achieved simply either by shaping the front face of the transducer or by adding a curved lens or mirror. While the advantage of these optical approaches is simplicity, the disadvantage is that the beam is focused at only one fixed depth. More sophisticated array processing techniques allow focusing over a range of depths. However, such arrays are expensive and complex, and there is a risk of artefacts.

Image quality

There is an ongoing debate about the most meaningful way of measuring and describing the quality of ultrasound scanning systems and, despite the existence of several national and international standards,[49] there is disagreement between expert groups. Much of the discussion centres round the poor correlation between users' perceptions of image quality and the measured performance values.

However, for IVUS systems, resolution is a key parameter, even if it is not the only one. For any two-dimensional ultrasound system the resolution will be a function of the orientation of the target. It would be expected that the resolution along the direction of propagation of the beams (the axial resolution) would be best and, typically, would have a value of 2–3 wavelengths. This is equivalent to 0.2–0.05 mm for equipment in the range 20–30 MHz. The resolution in the other two orthogonal planes will normally be worse and will depend on the depth as well as the type of focusing involved. This resolution typically has the same value as the beam width. If the beam is not circular in cross-section, as is the case for electronically-focused machines, then the resolution also depends upon orientation. It is not clear what relationship should be expected between such resolution values and clinical utility, except that better resolution should give better images that are easier to measure. It is not known what the resolution values of specific IVUS systems are, as manufacturers are generally reluctant to release such data.

In general terms, the historical development of IVUS has been in three technical stages:

(i) multi-element radial transducers
(ii) single element, mechanically rotated transducers
(iii) multi-element linear or phased arrays.

Type (i) systems were never available commercially, being developed as research tools only. Articles describing studies using both types (ii) and (iii) systems will be found in the clinical literature. The range of intravascular transducers that are, or have been, commercially available is summarised in *Table 1*.

Accuracy and reproducibility

The main role of IVUS in guiding interventional procedures is in the measurement of cross-sectional dimensions. The accuracy of measurement axially is largely an issue of measuring a radial distance and this has three potential sources of error:

- incorrect identification of the surfaces to be measured
- incorrect selection of the section to be measured
- incorrect assumption about the speed of sound in the material in question.

Errors of the first type are difficult to quantify, depend upon the skill of the operator and are likely to be random. However, since the blood-vessel wall interface is sharp and normally well-defined acoustically, experienced operators ought not to have major problems in most cases. It would be expected that better axial resolution would lead to sharper edge definition, thus reducing this error. However, the theoretical axial resolution of under 0.2 mm for frequencies of 20 MHz and above should be more than adequate for most purposes.

The second type of error will be important when the probe does not lie along the axis of the main vessel. This will lead to oblique sections being measured. The errors will have a systematic component and will normally lead to an over-estimate of the dimensions in question. It might be expected that they would be worst when there is considerable tortuosity or when a stiff cable is used. Mechanical devices are at a disadvantage here.

The third type of error will be systematic and small, provided that the temperature of the blood is constant. Equipment is calibrated using an assumed value of 1540 m s^{-1} but blood has a slightly higher speed of sound that this. This is only likely to lead to a 1–2% dimensional error, which is probably insignificant.

Any differences in clinical effectiveness between the various machines are unlikely to result from variations in the intrinsic accuracy of the equipment. Studies using phantoms[50–51] have demonstrated the accuracy of the technology *in vitro*. It is feasible that the improved image quality that might be expected from using better quality higher frequency probes will be manifest in improved reproducibility rather than in absolute measurement accuracy. The reproducibility, or precision, of any method is of great importance. Two or more measurements should be made from the same subject so that the similarity of duplicate measurements can be assessed. The worse the agreement between the two measurements, then

TABLE 1 *Range of intravascular ultrasound transducers*

Manufacturer	Frequency	Catheter size	Transducer type
Boston Scientific	20 MHz	4.9 F	Mechanical
Boston Scientific	30 MHz	3.5 F	Mechanical
Endosonics	20 MHz	3.5 F/5 F	64 element array
CVIS	30 MHz	2.9 F	Mechanical
CVIS	30 MHz	3.5 F	Mechanical
CVIS[a]	20 MHz (Fwd)		Mechanical
CVIS	30 MHz	5 F	Mechanical (mirror)
CVIS	25 MHz	3.9 F	Mechanical

[a] *This device has the unusual feature of not firing exactly sideways but rather at a forward angle. This allows imaging of the lesion ahead, even it is too small for the device to pass through. However, it introduces both systematic and random errors in measured dimensions*

the greater any real change must be before it can be classified as a real change and not one caused by poor reproducibility. Poor inter-observer reproducibility could mean that the decision reached by different observers differs, in turn leading to different management decisions and, potentially, different outcomes for the patient. In this review, the literature on the *in-vivo* reproducibility of the measurements made during IVUS-guided interventions is investigated.

Decision-analytic modelling

Decision-analytic modelling[52] is used to determine the optimal course of action when faced with options with different outcomes and associated risks. It has been widely used in the clinical field and is increasingly used as a vehicle for economic evaluation of diagnostic and therapeutic procedures. It is particularly useful when evidence from controlled clinical trials is either unavailable or is of a restricted nature, as was likely to be the case in this review.

A decision model[53,54] can be used to synthesise data from a variety of sources, including controlled trials, observational studies, literature reviews and expert opinion. Models have been used to pre-test hypotheses when planning trials,[52] and to adapt the results of trials to new care-settings,[55] new patient populations[55] or new time horizons.[55] Models should be treated with caution when used in place of trials[56] but, when based on the best available data, they can be useful to decision makers. Sensitivity analysis must be performed to test the robustness of the results in response to changes in key assumptions or parameters. Sensitivity analysis can also be used to determine whether or not a technology is clearly dominant[57] compared with the alternatives, by making comparisons at the extremes of its performance. A technology is dominant if it is both more effective and less expensive in all scenarios. The alternative technology is dominant if the technology of interest is less effective and more expensive in all scenarios. In the situation in which the technology is more effective but also more expensive, cost-effectiveness analysis is then required. In such circumstances, the decision rule is set to define a target norm below which the technology is cost-effective, for example, a limit of £10,000 per quality-adjusted life year (QALY) gained. If, in all circumstances, the cost-effectiveness ratio is below the target level, then a robust conclusion of cost-effectiveness has been demonstrated.

In the field of medical imaging, the absence of data from good quality trials in many areas presents opportunities to use modelling to make the best use of the data that are available. In this particular review, economics are added to studies concentrating on clinical endpoints and the findings of short-term trials are projected to determine their implications over a longer period. The use of a short-term decision-tree model and extrapolation of long-term effects will be a preliminary approach to assessing the economic impact of IVUS. More sophisticated approaches to decision modelling, such as a Markov approach or discrete event simulation, would be needed to extend the model to cover patient lifetimes. These approaches are not used in this study because it was expected that data on the costs and outcomes of the use of IVUS obtained from the systematic review would be limited in terms of scope and length of follow-up. There are, however, existing models that have been developed to assess the long-term outcomes of cardiovascular interventions other then IVUS, using long-established and accepted models of cardiovascular disease. These models utilise the intermediate clinical outcomes that are reported in IVUS studies and allow information on long-term impact to be acquired even in the limited time available.

Conclusion

The simple evaluative framework appropriate to imaging technologies has been outlined above, the technology of IVUS has been described and related to the clinical context of interventional cardiology and the role of decision-analytic modelling has been described and justified. The research questions addressed in this review are clarified in the next chapter.

Chapter 2

Research questions

The following applications of the technology are concentrated on in this study.

- IVUS-guided primary stenting.
- IVUS-guided optimisation of PTCA.
- Other IVUS-guided coronary interventions.
- IVUS-guided therapy for in-stent restenosis.

The questions addressed in each case are as follows.

- Does IVUS guidance improve outcomes compared with the procedure without IVUS guidance? The outcomes of interest are angiographic restenosis at 6 months and MACE within 1 year.
- Is the technology cost-effective in the application?
- Is there any morbidity associated with the use of IVUS?
- What is the failure rate of IVUS examination in the application?
- What, in the case of IVUS-guided therapy for in-stent restenosis, is the therapeutic impact of IVUS?

In applications in which IVUS guidance is used, it is usual to make quantitative measurements of luminal area or diameter using IVUS. The final question addressed is:

- What is the *in vivo* intra- and inter-observer reproducibility of measurements made using IVUS?

Chapter 3

Review methods

This chapter, in which the methodology of the review is described, is divided into two parts. In the first, the literature review is described in terms of the search strategy, exclusion criteria, assessment of relevance and validity, and data extraction and synthesis. The second part is concerned with decision-analytic modelling.

Literature review

Search strategy

To address the research questions presented in chapter 2, four separate searches were undertaken. The individual strategies are described below.

IVUS-guided interventions

A systematic search of the literature was conducted, including electronic bibliographic databases and the Internet; to ensure an exhaustive search of the literature, bibliographic lists and non-indexed journals were search by hand and leading experts in the field were contacted.

The results of all searches were added to a database maintained in the Reference Manager™ (Research Information Systems Ltd) bibliographic database software package. There was significant overlap between the various data sources and in order to avoid studies being added to the database repeatedly, the following hierarchy of sources was defined (only the retrieval corresponding with the first source on the list was retained):

- MEDLINE
- EMBASE
- BIDS Science Citation Index
- BIDS Index of Scientific and Technical Proceedings
- BIDS Compendex
- BIDS Page One
- The Cochrane Library
- Inside (British Library)
- Internet
- Handsearching and contacting experts.

Electronic bibliographic databases The first stage of the literature review concentrated on the identification and retrieval of easily accessible, published data.

The following databases were searched, using the search strategies presented in appendix 2. The output of these searches was downloaded into Reference Manager for further analysis.

- MEDLINE
- EMBASE
- BIDS
  - Science Citation Index
  - Index of Scientific and Technical Proceedings
  - Engineering Compendex
  - Engineering Page One

In order to maximise the recall from these sources, separate search strategies were compiled taking into consideration the capabilities and limitations of each search interface. All articles published from 1990 to the end of 1998 were included. This corresponds with the period from the introduction of the technique to the last full year during the period of this project. To ensure that all studies published up to this date were available in the databases, the searches were re-run in March 1999 to allow for delays in updating studies, particularly in MEDLINE.

In addition two further electronic sources were searched.

- The Cochrane Library
- Inside (British Library)

For these sources, less sophisticated searches were conducted (see appendix 2) and the results were not automatically downloaded into Reference Manager. The results were manually compared against all inclusion criteria and those references already in the Reference Manager database, so that only those likely to be of relevance and not already identified were included.

The Internet This allows access to an expanding volume of information. The uncontrolled nature of the medium means that the quality of information available is variable, and sources may appear and disappear unpredictably. Although there are a variety of indexing services and search facilities available, and some concentrate on cataloguing quality medical material,[58] identifying useful and valid sites can be very difficult. To ensure that a systematic review incorporates the most up-to-date

information and results that are not published in any other form, a thorough search of the Internet is essential. Articles have been published that suggest approaches to identifying and retrieving information in a systematic, rigorous and effective manner.[59–60] These approaches were adapted and developed for medical imaging as described in appendix 3.

Handsearching of bibliographic lists and non-indexed journals The reference lists of all retrieved articles were handsearched to identify any additional articles. The source journals of all cited articles were identified, and a list compiled of those that were not indexed in the electronic sources already searched. Relevant books were noted but were neither followed-up nor included in the review, as it was unlikely that any high quality primary research would be reported only in textbook form.

Only journals not indexed by one of the main electronic databases (MEDLINE or BIDS) were handsearched. Since high-recall search criteria had been used, additional resources searched, and experts consulted, it was considered that omitting a handsearch of indexed journals would have little effect on the results. In addition to identification from reference lists of retrieved articles, non-indexed journals were identified from:

- Ulrich's periodical database
- Publist
- Science Citation Index: lists of cited references from relevant articles
- Internet websites
- advice from experts.

Contacting experts From conference proceedings identified from searching Science Citation Index and Index of Scientific and Technical Proceedings, 14 leading researchers were contacted about 50 abstracts that covered some of the major studies in progress, including CRUISE (Can Routine Ultrasound Influence Stent Employment?),[61] AVID (Angiography Versus Intravascular ultrasound Directed coronary stent placement),[62] SIPS (Strategy of ICUS-guided PTCA and Stenting)[63] and OPTICUS (OPTimization with ICUS to reduce stent restenosis).[64] In addition, letters were sent to the 15 most active cardiology centres (worldwide) requesting any information on unpublished or incomplete studies. The aim of this strategy was to acquire information about the most recent research and unpublished, or grey, literature. Articles identified in this way covered the years 1990–99.

Control arm articles

To address the first research question presented in chapter 2 (Does IVUS guidance improve outcomes compared with the procedure without IVUS guidance?), it was necessary to seek evidence not only on IVUS-guided interventions but also on those interventions without the IVUS guidance. This is described here as the control arm of the review. The ideal study sought for the control arm of this comparison would be a prospective, controlled trial covering the intervention both with and without the use of IVUS. No separate search was performed to identify such articles, as they would have been retrieved in the search described above. In our previous reviews of medical imaging topics,[6,65] however, little evidence had been found arising from controlled trials. To provide further evidence for the control arm, a separate search was used to identify comparable studies that did not involve IVUS guidance. A wide range of technologies was considered that could contribute to the control arm but it was decided to limit the search to PTCA with or without the addition of coronary stenting. This was to ensure that the studies had been performed in approximately the same period as those on IVUS-guided interventions. This search included MEDLINE and the Cochrane Library, incorporated a previously recommended substrategy that identifies randomised controlled trials (RCTs)[66] and was limited to meta-analyses. The searches were from 1990 onwards and were limited to English language articles involving humans. The search strategies are included in appendix 2. In addition, the website of the Wessex Institute for Health Research and Development[67] was searched for relevant Development and Evaluation Committee (DEC) reports.

Additional topics

Two further topics related to the role of IVUS were covered: in-stent restenosis, and reproducibility. For these topics, searches were made of our complete Reference Manager database of articles on IVUS-guided interventions. In this database, a keyword field was available containing medical subject heading (MeSH) terms from MEDLINE or keywords allocated by the individual electronic databases.

For in-stent restenosis and reproducibility, the Reference Manager database was searched by title, abstract and keywords as indicated in appendix 2. A single search of Reference Manager acted as a good proxy for the specific searches of six individual electronic databases. The

reference lists of these articles were handsearched for further relevant articles. All articles retrieved as candidates for inclusion in other parts of the review were handsearched for relevant information or references to studies of reproducibility and its synonyms.

Economics

Articles relating to the cost implications of IVUS-guided and non-IVUS-guided interventions were identified during assessment for inclusion in other parts of the review.

Exclusion criteria

IVUS-guided interventions

Three sets of predefined exclusion criteria were applied in sequence.

Electronic exclusion criteria Full reports of original studies with patient-based information were required, so the following preliminary exclusion criteria were applied using the classifications available in each database:

- review articles
- editorials
- letters
- case reports
- non-human studies (these include animal, *in vitro*, phantom and post-mortem studies)
- conference proceedings.

Manual exclusion criteria Subject-specific criteria for exclusion were applied and the preliminary exclusion criteria were re-checked. The following subject-specific exclusion criteria were applied in order, so that only the first applicable criterion was noted (in many cases more than one criterion was suitable but to save time only the first was used):

- not coronary arteries
- intensive care units (often returned by searches for ICUS)
- not IVUS
- Doppler only
- transplant recipients
- technical performance
- therapeutic or diagnostic use of IVUS
- fewer than ten patients included
- radial catheter approach (include only femoral approach)
- only one named coronary artery included.

If no abstract was available or insufficient information was given, the full article was retrieved and the exclusion criteria applied.

Final criteria Full copies of articles not excluded at the previous stage were acquired. All the exclusion criteria previously applied were re-applied to the full article. The following exclusion criteria were then applied to ensure that articles were indeed suitable for inclusion:

- not an IVUS-guided intervention
- registry data
- safety data.

Non-English language literature was retrieved but the full exclusion criteria were only applied to candidate articles in the areas of IVUS-guided stenting or angioplasty. The exclusion criteria were applied to the English abstract, if available, or to the full article prior to translation. Articles satisfying the preliminary criteria were translated in full, as were those for which a decision could not be made from the untranslated text.

Control arm articles

All articles except RCTs and systematic reviews were excluded and then the electronic and manual exclusion criteria described above for IVUS-guided interventions were applied. The criterion requiring that IVUS be performed was not applied.

Additional topics

In-stent restenosis The exclusion criteria described above for IVUS-guided interventions were applied. Any remaining articles were excluded if they did not consider the treatment of in-stent restenosis.

Reproducibility All articles were subjected to the electronic and manual IVUS-guided exclusion criteria. Two team members judged the remaining articles against the following exclusion criteria:

- no reproducibility results reported
- not native coronary vessels (e.g. grafts or cardiac transplants)
- reported reproducibility results refers to angiography not to IVUS measurements
- measurements reported do not include diameter or area
- measurements not reported for both lesion and reference segments
- intraobserver comparison made by measuring twice on the same image
- only correlation or linear regression methods used to express intraobserver and interobserver variability.[68,69]

Economics

The exclusion criteria described above for IVUS-guided interventions were applied. Remaining articles were excluded if they did not include a health economics analysis.

Assessment of relevance and validity

IVUS-guided interventions

The possible roles for IVUS in guiding coronary interventions are illustrated on the decision tree in *Figure 1*.

Three procedures that may be guided by IVUS are stenting, angioplasty (PTCA) or atherectomy (ROTA, DCA and excimer laser coronary atherectomy (ELCA)). IVUS may be used for guiding the chosen procedure but it might also be used before the intervention to select the procedure. Overall, eight possible combinations for the use of IVUS are suggested in *Figure 1*. Evidence was sought in the literature relating to the use of IVUS in these roles.

An assessment of validity was performed by assessing the articles against the five criteria shown in *Table 2*; these were agreed by panel discussion.

Control arm articles

Systematic reviews of stenting or PTCA were critically appraised by one member of the study team who made a judgement of the individual quality of each review by applying criteria derived from the NHS Centre for Reviews and Dissemination, York,[66] and from Sackett and colleagues.[70] In this way, the most valid and up-to-date reviews of primary RCTs were identified. Two team members then critically appraised the individual primary trials listed in these reviews. The articles were assessed against the first four criteria shown in *Table 2* to assess validity. Studies were excluded if IVUS guidance was planned for some of the patients as part of the protocol. To minimise heterogeneity and improve comparability with the articles included on IVUS-guided interventions, articles were included only for patient groups with the following characteristics:

- more than one named coronary artery studied
- native coronary vessels
- elective stenting procedure
- stable or unstable angina
- absence of AMI
- not chronic or total occlusion.

Additional topics

In-stent restenosis No further assessment of validity was performed.

Reproducibility A series of IVUS images is acquired while the catheter is drawn slowly

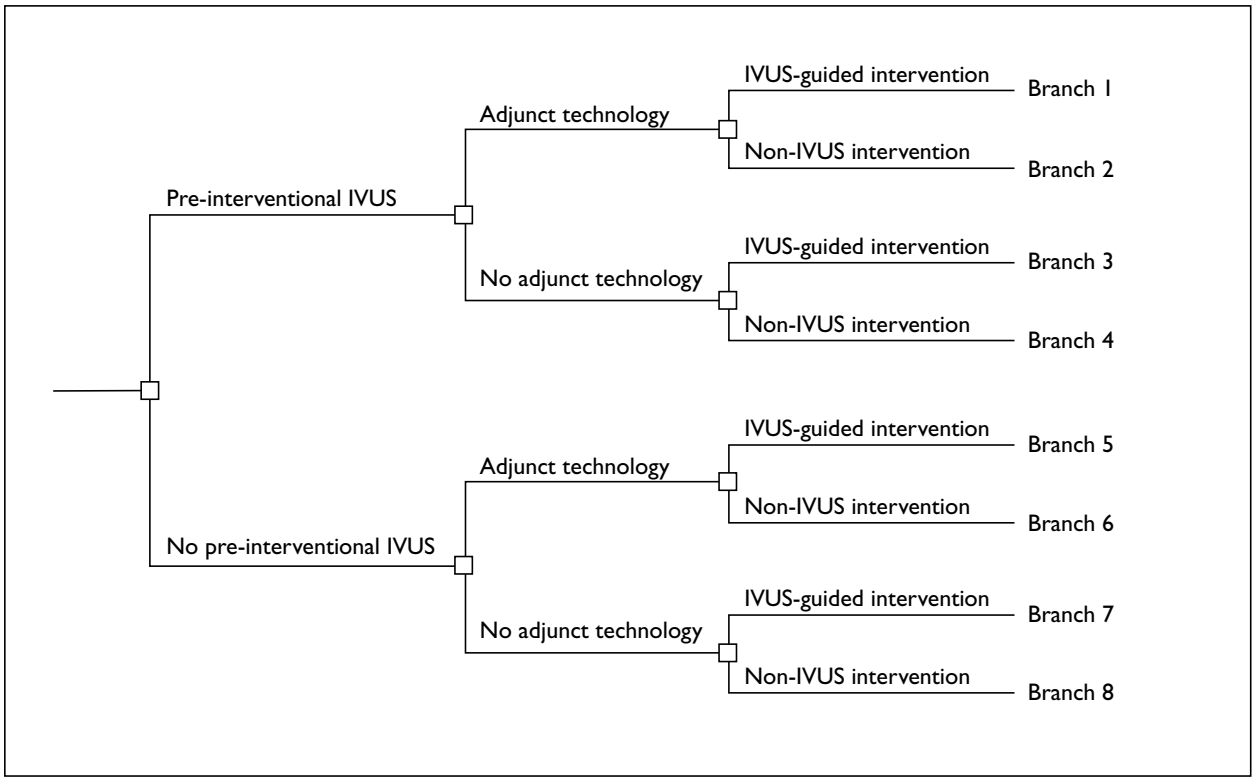

FIGURE 1 *Decision tree representing the possible roles for IVUS in guiding coronary interventions*

TABLE 2 *Validity criteria for inclusion in review of intravascular ultrasound-guided interventions*

Characteristic	Inclusion criterion	Reasons for exclusion (see *Table 42*)
Sets of patients from same centre	If some members of patient groups are same in two or more articles, include only largest study If patient groups clearly different, include all articles	Patient group: overlap
Percentage followed-up	Include if ≥ 85% of patients followed-up	Clinical follow-up: < 85% Angiographic follow-up: < 85%
Follow-up time	Restenosis: include if follow-up time specified at outset is 6 months (may be some variation in actual period) Clinical follow-up: include if any follow-up	Clinical follow-up: none Angiographic follow-up: none or not 6 months
Study information	Restenosis: at least angiographic criteria definition specified Clinical: at least clinical event rate specified	Clinical follow-up: too little information Angiographic follow-up: too little information
Percentage of patients receiving IVUS-guided intervention	Include if IVUS guidance planned for all patients as part of protocol and percentage of those receiving IVUS is specified	Not ITT

through the vessel; this is known as a pullback. A proper assessment of repeated measurements by the same observer would use two or more images from different pullbacks, rather than repeating the measurement on the same image from a single pullback. The latter could reduce the apparent variation of the whole imaging and measurement process, while the former demonstrates the consistency of interpretation for repeated imaging. Although the same comment should also apply to interobserver comparisons, in practice most interobserver assessments use the same image, so the effects of interobserver rather than interexamination differences are determined.

Studies were included if:

- intraobserver comparison measurements were made on different images from two pullbacks
- interobserver comparison was made by measuring twice on images from the same pullback
- mean and standard deviation (SD) of paired differences was used to express intraobserver and interobserver variability.[68,69]

The following study features were noted:

- measurements made in presence of contrast medium
- measurements made pre-intervention, post-intervention or both
- automatic or manual border delineation.

Economics

Studies were included if all four of the following criteria were satisfied:

- type of economic analysis was correctly chosen and designed
- outcome indicator was appropriate
- cost analysis was correctly conducted
- sensitivity analysis was carried out.

Guidance on what was appropriate or correct was taken from published sources.[71–74]

Data extraction

IVUS-guided interventions

Articles on IVUS-guided interventions required more clinical interpretation than any of the other groups of articles. Checklists were designed (see appendix 4) to cover study details, patient characteristics and results. These were completed for each article independently by two clinician team members and the main reviewer. Consensus was reached on any disagreements.

Control arm articles
Results were summarised from the primary RCTs by one team member.

Additional topics
Data were extracted and summarised by one team member.

Economics
Data were extracted and summarised by one team member.

Data synthesis

When data were available from the articles about the numbers of patients in a category, results from all included studies were pooled to calculate an overall event rate, or proportion. For example, the restenosis rate is the absolute number of restenoses divided by the total number of lesions from all the relevant studies. The standard error (SE) for the calculated proportion[69] was found from:

$$\mathrm{SE} = \sqrt{\frac{P(1-P)}{n}} \qquad (1)$$

where P is the calculated proportion and n the total number of patients included.

The 95% confidence interval (CI) was ± 1.96 SE.

The 95% CI for the difference between the proportions seen in the two arms of the review was found from ± 1.96 SE, where the SE is given by:

$$\mathrm{SE}(P_1 - P_2) = \sqrt{\frac{P_1(1-P_1)}{n_1} + \frac{P_2(1-P_2)}{n_2}} \qquad (2)$$

No test was applied to determine the statistical significance of differences between the arms of the review because of the differing eligibility criteria in the included articles.

When less than two articles presented numerical results, results were synthesised by qualitative descriptions or by using the decision-analytic model.

Reproducibility
The worst reported reproducibility was taken as a limiting value and used to estimate the minimum detectable change.[69] This was estimated from the SD of differences between measurements using the expression, 1.96 × SD.

Decision-analytic model

Design of the model
The expert panel drafted a decision tree. The tree represented all the possible pathways that could be taken by a patient from their presentation to a final health outcome. The tree underwent amendment several times to ensure that it fitted the clinical protocols described in the literature and was a generic tree applicable to practice worldwide. The agreed tree is shown in *Figure 2*.

Each branch point on the tree is a decision point representing either a clinical decision or a chance event. Final outcome points are represented by a triangle. A probability was assigned to each event and a cost to each of the terminal branches of the tree. The software package Data™ 3.0 (Treeage Software Inc.) was used to run the completed model. Modelling gave the cost associated with each of the two major branches of the tree, based on the probabilities and costs supplied. These modelled costs relate only to events later in the tree and do not include the cost using the technology itself. This will be termed the 'outcome cost' to distinguish it from the 'intervention cost'. The incremental intervention cost of adding IVUS guidance to an intervention was found separately. The total incremental cost per patient was calculated from the sum of the incremental outcome cost and the incremental intervention cost. The analysis was performed from the perspective of the healthcare provider.

An incremental cost-effectiveness ratio (ICER) is defined as the difference in cost divided by the difference in effect between the alternatives under comparison.[75] For this analysis, two expressions of cost-effectiveness ratio were used. First, the ICER measured in £/restenosis event avoided, was defined as:

$$\mathrm{ICER}_{\mathrm{re}} = \frac{\text{(Total incremental cost per patient)}}{\text{(Absolute reduction in restenosis rate)}} \qquad (3)$$

where the absolute reduction in restenosis rate was the difference in the probability of restenosis assigned to each arm of the decision tree.

Second, the ICER measured in £/QALY gained was defined as:

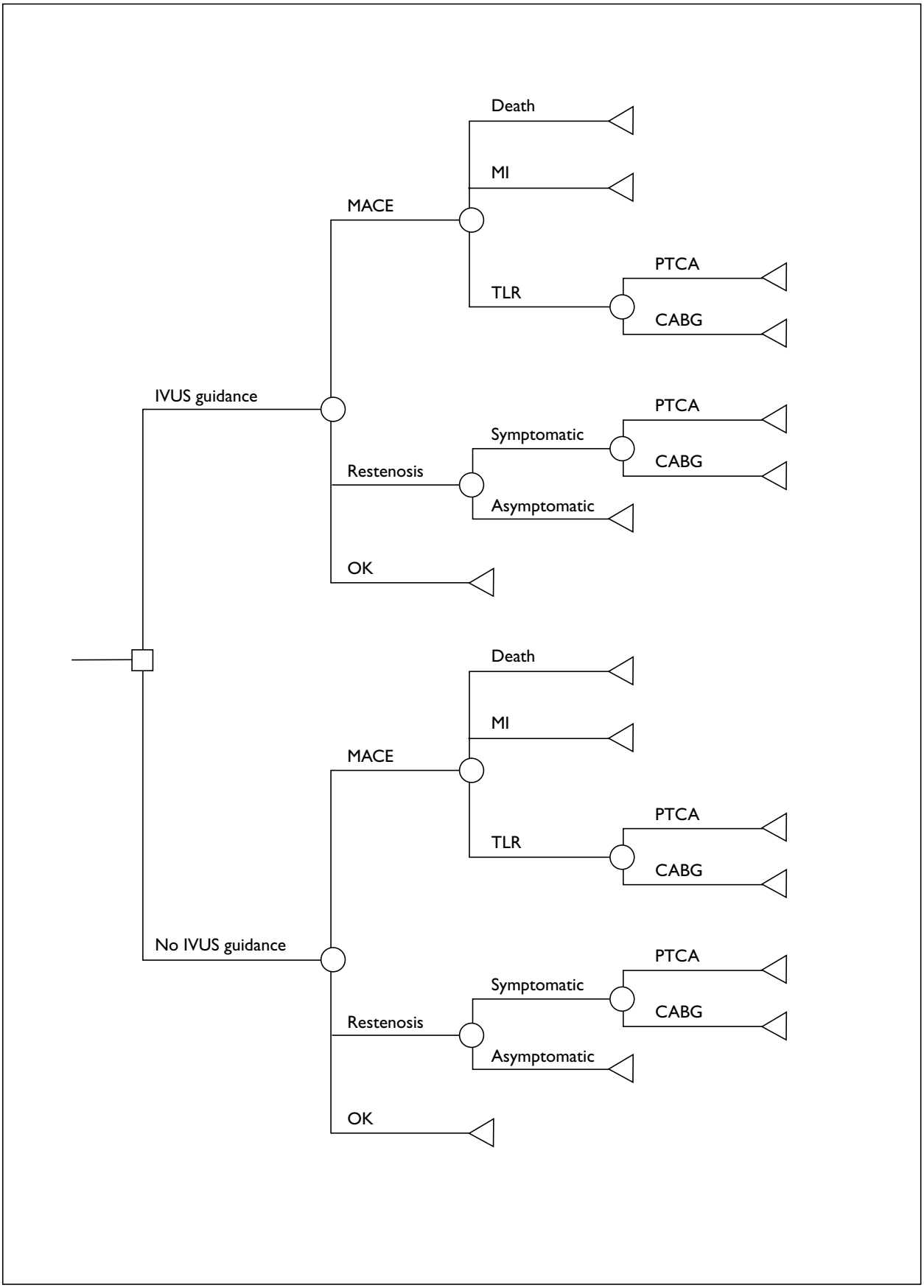

FIGURE 2 *The decision tree used for decision-analytic modelling of IVUS-guided interventions. Each branch point on the tree is a decision point representing either a clinical decision (□) or a chance event (○). Final outcome points are represented by a triangle (◁)*

$$\text{ICER}_{\text{QALY}} = \frac{\text{(Total incremental cost per patient)}}{\text{(QALY gain)}} \quad (4)$$

where the QALY gain was determined by extrapolation from the reduction in restenosis rate to long-term outcome. The QALY is widely used in economic evaluation[76] to incorporate both improvements in life expectancy and in health-related quality of life.

Data for the model from the literature

Probability data were sought primarily from the articles included in the literature review. Values were required for the procedural complication rate, 6-month angiographic restenosis rate, rate of symptomatic/asymptomatic restenosis, 6-month MACE rate (death, Q-wave MI, non-Q-wave MI and revascularisation) and QALY gains from avoiding such events.

The costs of events in the final branches of the decision tree were taken from McKenna and colleagues,[77] updated to 1998 values. It was assumed that all CABG procedures in symptomatic branches were elective and that all CABG procedures in the MACE branch were emergency operations. It was also assumed that there would be no treatment, and no cost, associated with the asymptomatic restenosis branches. Similarly, no cost was associated with the 'OK' branches. Longer-term effects of reducing restenosis, thus possibly affecting future healthcare consumption, were not taken into consideration in the analysis.

Empirical study

Intervention costs were determined as follows:[78]

(i) clinical activities associated with following the pathway were identified (including procedures, hospitalisations)
(ii) associated healthcare resources were identified (including staff time, theatre time, consumables, drugs)
(iii) unit costs were determined
(iv) total costs were estimated by multiplying resource use by unit costs.

Data were sought from the articles included in the literature review and from a small study conducted for the model. Resource values were required for: numbers of stents, balloons, catheters and other consumables used; procedure time; staff time; IVUS equipment used; capital costs. Also sought were the unit costs associated with each resource. The procedural time was obtained from the management database in the catheterisation laboratory and represents the total time spent by the patient in the laboratory.

To supplement the health economics information available from retrieved articles, data were obtained from a study of IVUS-guided stenting performed at the Leeds Teaching Hospitals NHS Trust.[79] A matched group of patients who had undergone routine stenting without IVUS guidance in the Leeds Teaching Hospitals was identified. It was possible to match 19 patients stented without IVUS guidance with 19 patients stented with IVUS guidance. The matching characteristics are shown in *Table 3*.

The records of the matched patients were re-evaluated by the clinician involved in the original study to determine the clinical circumstances of the patients. Complications that were not a direct consequence of the use of IVUS were also identified. Of the 38 patients, five in the IVUS group and eight in the non-IVUS group underwent single vessel, single stent implantation. Analysis of this subgroup was not performed because of the small numbers of patients involved.

TABLE 3 *Matching characteristics for the empirical comparison of intravascular ultrasound-guided interventions with non-guided interventions*

Matching characteristic	IVUS group	Non-IVUS group
Gender	63.2% male	63.2% male
Pre-procedure diagnosis	84.2% stable angina	84.2% stable angina
Procedure status	89.5% elective	89.5% elective
Consultant, 1st operator	31.6%	31.6%
Consultant, 2nd operator	68.4%	68.4%
Other, 1st operator	52.6%	36.8%
Other, 2nd operator	21.1%	0%
Number of 1st operators	5	6
Number of 2nd operators	4	6
Mean age (years)	61.9 ± 2.1	61.6 ± 2.1

The cardiologist involved in the study and the main reviewer recorded the procedural details and the time spent in the catheterisation laboratory for each group. Estimates of staff resource use were calculated from the procedural time, using hourly rates[80,81] and assuming that four staff were present in all cases: a nurse, a technician, a radiographer and a cardiologist or radiologist.

Information about consumables used was extracted from the Leeds Teaching Hospitals NHS Trust database for both groups of 19 patients and expressed in terms of the use per patient. Some of the articles included in the review also gave information in the number of stents used, with or without IVUS guidance. When figures were reported per lesion, they were converted to per-patient equivalents, and the average value of the reported and Leeds Teaching Hospitals NHS Trust figures was calculated for use in the analysis. The 1998 figures for unit consumables costs were obtained from the Leeds Teaching Hospitals NHS Trust.

Capital costs are generally much less flexible in the short term than staffing and consumables – the sunk costs are incurred whether facilities are used or not – so changes in patient throughput do not change the accounting cost. In an organisation with constrained resources, such as an NHS hospital trust, there is a real short-term economic cost of using space for catheterisation laboratories. This is the loss of the opportunity to use the space to provide services and health benefits to a different patient group – that is, the economist's concept of 'opportunity cost'.[82] In the longer term, this cost can be estimated as the annualised cost of replacing the facilities used. For large buildings, accounting conventions are used to allocate the capital replacement costs across departments using the facilities. In the Leeds Teaching Hospitals NHS Trust, facilities costs are estimated to be 40% of the staff costs for a service, and this approach has been used in our analysis. An estimate of the acquisition costs of IVUS equipment had to be made, as a manufacturer's price was not available. This is because the equipment is never sold independently but always as part of a contract for catheter supply. To produce an annual equivalent cost for the use of the equipment, a 5-year lifetime was assumed and the standard UK public sector discount rate of 6% applied.[57,83]

To calculate the cost per patient, the capacity of the catheterisation laboratories in terms of numbers of patients per year was estimated, assuming an equal capacity to treat all the patients with IVUS guidance. The incremental intervention cost per patient of performing the IVUS-guided intervention was found from the sum of the incremental costs of consumables, equipment, staff and facilities.

For convenience, the findings of the empirical study are presented in the same chapter as values for the model drawn from the literature (see chapter 4).

Calculation of probabilities

Outcome data relevant to the branches of the decision tree were extracted from articles included in the review. Probabilities for each branch of the tree were determined as follows.

IVUS-guidance branch

Probabilities for the occurrence of MACE, restenosis or a satisfactory outcome (designated 'OK' in the decision tree, *Figure 2*) were calculated for the patients in the included articles. If patients refused follow-up angiography, it was assumed that they had a satisfactory outcome unless a MACE was reported. The MACE rate used was a hierarchical one representing the number of patients, not the total number of events.

IVUS-guidance restenosis branch

The probabilities of the occurrence of angiographic restenosis, symptomatic restenosis, repeat PTCA and CABG were calculated for the total number of restenosis cases in the included articles. Symptomatic restenosis was defined as angiographic restenosis with accompanying angina. If no information was given about the number of re-interventions arising from restenosis, it was assumed that a single re-intervention was performed. When no information was given about the type of re-intervention, the number for each alternative was calculated assuming that the proportion of each type was the same as that given in articles that did provide the information.

IVUS-guidance MACE branch

The probabilities for the occurrence of death, MI and revascularisation were calculated for the MACE cases, excluding those already counted in the restenosis branch, in the included articles. In this case the total number of MACE events was used, not the hierarchical rate. Further, the probabilities for repeat PTCA and CABG were calculated for the number of patients in the revascularisation branch.

No IVUS-guidance branch

Probabilities for the occurrence of MACE, restenosis or a satisfactory outcome (designated 'OK' in the decision tree of *Figure 2*) were calculated in the same way as for the IVUS-guidance branch.

No IVUS-guidance restenosis branch

The probabilities for the occurrence of angiographic restenosis, symptomatic restenosis, repeat PTCA and CABG were calculated for the total number of restenosis cases in the included articles. In this case, because the articles for this branch did not differentiate between symptomatic and asymptomatic restenosis, it was necessary to make the assumption that those individuals who had angiographic restenosis with target lesion revascularisation (TLR) were equivalent to a group with symptomatic restenosis. If no information was given about the type of re-intervention, the proportions of each type were assumed to be the same as that for the corresponding part of the IVUS-guidance branch and numbers for each alternative were estimated.

No IVUS-guidance MACE branch

The same method was used as for the IVUS-guidance MACE branch. The probabilities for the occurrence of death, MI and revascularisation were calculated for the MACE cases, excluding those already counted in the restenosis branch, in the included articles.

The SE for each probability[84] was calculated using equation 1.

This allowed the calculation of 95% CIs (± 1.96 SE) for use in the sensitivity analysis (see chapter 7).

Extrapolation to long-term outcome

Only data relating to the intermediate clinical endpoint of angiographic restenosis were available from the literature. There was no published evidence on long-term survival or quality of life associated with the use of IVUS. The results of the model were extrapolated from the 6-month outcome to a long-term analysis. This was done by making use of information from a published article[85] on the long-term benefit of the use of stents compared with PTCA alone, expressed as a QALY gain. Assuming that all the long-term benefit of stenting arose purely from the reduced restenosis rate compared with PTCA alone, an estimate of the QALY gain per restenosis event avoided was made (QpR):

$$\text{QpR} = \text{QALY}_{\text{stents}} / (\text{absolute reduction in restenosis rate})_{\text{stents}} \quad (5)$$

This value was taken to be valid whatever method had been used to achieve the reduction in restenosis events, so:

$$\text{QpR} = \text{QALY}_{\text{IVUS}} / (\text{absolute reduction in restenosis rate})_{\text{IVUS}} \quad (6)$$

The absolute reduction in restenosis rate with IVUS guidance was found from the decision model and an estimated incremental QALY gain found by rearrangement of equation (6):

$$\text{QALY}_{\text{IVUS}} = \text{QpR} \times (\text{absolute reduction in restenosis rate})_{\text{IVUS}} \quad (7)$$

From equations (4) and (7), the long-term cost per QALY gained for IVUS is:

$$\text{ICER}_{\text{QALY}} = \frac{(\text{Total incremental cost per patient})_{\text{IVUS}}}{\text{QpR} \times (\text{absolute reduction in restenosis rate})_{\text{IVUS}}} \quad (8)$$

Threshold analysis was performed to determine the limits on cost-effectiveness. The cost-effectiveness limit was set to £10,000 per QALY gained.[86] Values were calculated by substituting in equation 8 for the reduction in restenosis rate and total incremental cost that would cause this threshold to be exceeded. Baseline values from the analysis were assumed for the other parameters in each calculation. Equation 8 was used to calculate values for the total incremental cost per patient, for a range of restenosis rates achieved with IVUS guidance, over the 95% CI for the restenosis rate without IVUS guidance. Again, the limit of cost-effectiveness was set to a long-term cost per QALY of £10,000.

Sensitivity analyses

Sensitivity analyses for both the empirical cost study and the decision-analytic model are described in chapter 7.

Conclusion

The methodology of the review, the literature search and the methods associated with the decision-analytic model have been described in this chapter. In the next chapter the results of the literature searches are analysed. Details of the studies satisfying the inclusion criteria are

presented followed by information drawn from the literature and other sources for inclusion in the decision-analytic model. Results that address the questions raised in chapter 2, that have been drawn from the literature or calculated using the model, are presented in chapter 6.

Chapter 4

Studies included in the review

This chapter is divided into three sections. In the first, for those with an interest in methodological issues associated with systematic literature reviews, detailed information is given about the numbers of papers considered and excluded at each stage of the search process. This is followed by detailed descriptions of the articles included in the review. Finally, the information extracted for use in the decision-analytic model is presented.

Detailed analysis of search methodology

IVUS-guided interventions

Electronic bibliographic databases The results of applying the search strategies to the main electronic bibliographic databases are shown in *Table 4*. The numbers of articles remaining after the exclusion of duplicates are presented in *Table 5*.

The results of applying the preliminary electronic exclusion criteria using the facilities provided by the electronic bibliographic databases are given in *Table 6*.

The results of applying the manual exclusion criteria are given in *Table 7* (exclusions) and *Table 8* (inclusions).

The results of applying the final exclusion criteria are given in *Table 9* (exclusions) and *Table 10* (inclusions).

Most non-English language articles were excluded (see *Table 9*) but exclusion was not for reasons of language. One article[87] in German was translated and then excluded as it did not include IVUS-guided intervention. Another,[88] in Danish, was translated and then excluded as it reported less than 6 months follow-up. Two articles[89,90] (one in Japanese and one in Spanish) satisfied all criteria except for the additional need for non-English language articles to be in the area of IVUS-guided stenting. They were not translated. One article[91] in Japanese presented incomplete restenosis rate results with no clinical follow-up and was not translated. A further seven articles were excluded without full translation being necessary.[92–98]

Other electronic databases One article[99] was identified from the Cochrane Library but could not be obtained. The search of Inside returned 66 articles not identified from the other electronic databases. Of these, 20 were published in 1999, seven were abstracts, 21 were articles in books, nine were review articles, six were excluded as not being IVUS-guided interventions and one was excluded as it did not involve the coronary arteries. Both the remaining articles were in Japanese: one[100] was a study of IVUS-guided

TABLE 4 *Number of articles retrieved from each database*

	MEDLINE	EMBASE	SCI	ISTP	Compendex	Page 1	Total
English	2246	2248	2663	243	271	131	7802
Non-English	391	330	195	11	7	0	934
Number in database	2637	2578	2858	254	278	131	8736

TABLE 5 *Number of articles remaining after exclusion of duplicates*

	MEDLINE	EMBASE	SCI	ISTP	Compendex	Page 1	Total
English	2246	493	1191	129	177	10	4246
Non-English	391	164	52	7	4	0	618
Number in database	2637	657	1243	136	181	10	4864
Percentage of those retrieved (*Table 4*)	100	25.5	43.5	53.5	65.1	7.6	55.7

TABLE 6 *Exclusions after application of preliminary electronic exclusion criteria – indicates that the electronic exclusion criteria could not be applied in these databases*

	MEDLINE		EMBASE		SCI		ISTP		Compendex		Page 1		Total	
	E	Non-E	E	Non-E	E	Non-E	E	Non-E	E	Non-E	E	Non-E	E	Non-E
Review	243	82	72	15	54	5	–	–	–	–	–	–	369	102
Editorial	27	2	8	2	28	1	–	–	–	–	–	–	63	5
Letter	22	0	6	0	12	0	–	–	–	–	–	–	40	5
Case report	317	95	81	31	0	0	–	–	–	–	–	–	398	126
Abstract	0	0	50	3	671	0	–	–	–	–	–	–	721	3
Non-human	375	11	83	14	0	0	–	–	–	–	–	–	458	25
Number excluded	958	182	285	64	765	6	–	–	–	–	–	–	2008	252
Total number excluded	1140		349		771		–		–		–		2260	
Total excluded as percentage of those in *Table 5*	43.2		53.0		62.0		–		–		–		46.5	

E, English; non-E, non-English

TABLE 7 *Exclusions after application of manual exclusion criteria*

	MEDLINE		EMBASE		SCI		ISTP		Compendex		Page 1		Total	
	E	Non-E	E	Non-E	E	Non-E	E	Non-E	E	Non-E	E	Non-E	E	Non-E
Not coronary arteries	488	85	107	38	107	13	33	5	27	3	4	0	766	144
Intensive care unit	53	5	2	4	7	0	8	0	30	0	1	0	101	9
Doppler	106	11	11	2	8	1	2	0	3	0	0	0	129	14
Review	34	16	14	8	83	8	3	0	19	0	0	0	118	38
Not IVUS	106	27	27	8	83	8	3	0	19	0	0	0	238	43
Transplant	78	6	8	4	32	4	2	0	0	0	0	0	120	14
Non-human	90	15	7	2	53	2	4	1	27	0	0	0	181	20
Technical	40	0	4	0	26	0	36	0	55	0	4	0	165	0
< 10 patients	30	7	5	4	3	1	2	0	0	0	0	0	40	12
Case report	0	0	3	1	12	0	0	0	0	0	0	0	15	1
Therapy	5	3	0	0	1	0	0	0	0	0	0	0	6	3
Conference	0	0	1	0	3	0	0	0	6	0	1	0	11	0
Radial approach	1	0	0	0	4	0	0	0	0	0	0	0	5	0
1999	2	0	7	0	26	0	4	0	0	0	0	0	39	0
Number	1032	175	196	71	399	41	120 excluded	7	177	4	10	0	1934	298
Total number excluded	1207		267		440		127		181		10		2232	
Total excluded as percentage of those in *Table 5*	45.8		40.6		35.4		93.4		100		100		45.9	

E, English; non-E, non-English

TABLE 8 *Numbers remaining after application of manual exclusion criteria*

	MEDLINE	EMBASE	SCI	ISTP	Compendex	Page 1	Total
English	256	12	27	9	0	0	304
Non-English	34	29	5	0	0	0	68
Number remaining	290	41	32	9	0	0	372
Total remaining as percentage of those in *Table 5*	11.0	6.2	2.6	6.6	0	0	7.7

TABLE 9 *Exclusions after application of final exclusion criteria*

	MEDLINE		EMBASE		SCI		ISTP		Total	
	E	Non-E	E	Non-E	E	Non-E	E	Non-E	E	Non-E
Not IVUS-guided intervention	200	26	7	23	12	5	8	0	227	54
Registry	0	3	0	0	1	0	0	0	1	3
Safety	4	0	0	0	1	0	0	0	5	0
Number excluded	204	29	7	23	14	5	8	0	233	57
Total number excluded	233		30		19		8		290	
Total excluded as percentage of those in *Table 5*	8.8		4.6		1.5		5.9		6.0	

E, English; non-E, non-English

TABLE 10 *Numbers remaining after application of final exclusion criteria*

	MEDLINE	EMBASE	SCI	ISTP	Total
English	52	5	13	1	71
Non-English	5	6	0	0	11
Number remaining	57	11	13	1	82
Total remaining as percentage of those in *Table 5*	2.2	1.7	1.0	0.7	1.7

optimal directional coronary atherectomy and the other[101] was a study of IVUS-guided stenting that only reported the angiographic restenosis rate at 3 months.

Inside included 15 journals (*Table 11*) that were not indexed in the main bibliographic databases. Two articles that satisfied all the inclusion criteria for the review were found from these journals. Where it is noted in the table that the journal is 'indexed selectively', it means that the journal is indexed in one of the bibliographic databases but the indexing is incomplete. Articles were identified from the search of Inside and not from the bibliographic database. Inside was also the source of a newly published article on an RCT which was not yet available in the main electronic databases. This trial was included in the review as it addressed one of the questions.

Internet The Internet search covered 66 medical sites or databases identified from 15 medically-related organised gateways or a search using the Copernic search engine (see appendix 3). A summary of these 66 sites and the results retrieved appear in *Table 12*.

The results shown were clinically relevant and not already identified from previous searches. Four

TABLE 11 *Fifteen journals identified from the British Library* Inside *database as not indexed, or incompletely indexed, elsewhere*

Journal	Notes
Intravascular Imaging	Commentary and reviews
Current Techniques in Interventional Radiology	Annual
Cardiovascular and Interventional Radiology	Indexed on MEDLINE and EMBASE, except vol 20 suppl 1
Journal of Clinical Engineering	Indexed on EMBASE up to 1995
Fundamental and Clinical Cardiology	Irregular publication, incorporating books
Developments in Cardiovascular Medicine	Irregular publication, incorporating books
Kardiologia Polska	Polish; indexed selectively on EMBASE
Journal of Nihon University Medical Association	In Japanese with English summaries
Journal of Tokyo Womens Medical College	In Japanese; indexed selectively on EMBASE
Verhandlangen der Deutsschen Gesellschaft fuer Pathologie	Indexed selectively on MEDLINE
Annales de Cardiologie et d'Angeiologie	Indexed selectively on MEDLINE and EMBASE
Arquivos Brasileiros de Cardiologia	Indexed selectively on MEDLINE and EMBASE
Quarterly Journal of Cardiology	Not on Ulrich or Publist (periodical databases)
Tokyo Jikeikai Medical Journal	Indexed selectively on EMBASE
Etudes et Evaluation Cardiovasculaires	Not on Ulrich or Publist (periodical databases)

applicable items of information were found: one journal that focused on diagnostic sonography; two[102,103] ongoing trials in IVUS-guided stenting, and one completed trial (OPTICUS).[104] *Journal of Diagnostic Medical Sonography* was searched on-line and one candidate article was suggested but we were unable to obtain it. No additional information on the trials could be obtained in time for inclusion in this review.

Handsearching of bibliographic lists and non-indexed journals The titles of the non-indexed journals identified by searching reference lists of all retrieved articles are shown in *Table 13*.

No attempt was made to obtain copies of journals not included in either Ulrich or Publist, as experience has shown unlisted journals to be unavailable. Journals indexed on one of the electronic databases only before a particular date were assumed to have ceased publication, unless Ulrich or Publist gave further information. The remaining publication, *Polski Przeglad Chirurgiczny*, a Polish journal with English and Russian summaries, was not searched because it was unavailable.

The non-indexed journals identified by the other searches are shown in *Table 14*. All except *Journal of Diagnostic Medical Sonography* (identified on-line) were identified from the periodical databases Ulrich or Publist. Of the 22 publications identified from Ulrich or Publist, two were searched and eight had ceased publication or were considered irrelevant to the review by the panel. A panel decision was made that it would be too time-consuming to locate the remaining 12 journals for handsearching. Their publication frequency ranged from bimonthly to irregular.

Contacting experts From the canvassing of authors and centres involved in IVUS, three replies were received. These supplied the full draft version[105] of the CRUISE study, a personal database of IVUS articles, and a promise of a submitted manuscript of the SIPS study once it had been accepted. No additional relevant articles were found from the personal database and the manuscript had not been received at the time of writing.

Control arm articles

A total of 3057 articles were identified in the Cochrane Library: 27 in the Database of Systematic Reviews; 34 in the Database of Abstracts of Reviews of Effectiveness (DARE); 2968 in the Clinical Controlled Trials Register; and 28 health technology assessment reports. No applicable systematic reviews were found. Limiting the search to articles of PTCA with coronary stenting, two articles were identified from DARE and four from the health technology assessments section. One study was identified from both sources, so five[106–110]

TABLE 12 *Summary of Internet search results*

Gateway	Site	Address	Results
Surgical Internet Information Gateway www.rcsed.ac.uk/gateway.htm	Bandolier	www.jr2.ox.ac.uk/Bandolier	None
UK Health Centre www.healthcentre.org.uk/	Chest and Cardiovascular Medicine Index	www.healthcentre.org.uk	None
	Cardiovascular disorders	/hc/clinic/websites/heart.htm	None
	CHAIN	www.nthames-health.tpmde.ac.uk/chain/chain.htm	None
	Current Controlled Trials	www.controlled-trials.com	None
	UK Research Councils	www.nerc.ac.uk/research_councils	None
	HSTAT	www.text.nlm.nih.gov/ftrs/gateway	None
Achoo Healthcare Director www.achoo.com	Community Health Research Unit	www.uottawa.ca/academic/med/epid/chru.htm	None
	Medical Ultrasound Imaging www Directory	home.att.net/~don.christopher/ultrasound.htm	*Journal of the Society of Diagnostic Medical Sonographers*
	National Guideline	www.guideline.gov/index/asp	None
	Heart Beat (journal)	www.worldheart.org/heartbeat	None
Medical World Search www.mwsearch.com	AHA	www.amhrt.org	None
	Diagnostic Imaging (journal)	www.diag.com/subscribe.htm	Inaccessible
	USA – FDA News	www.fda.gov/opacom/hpnews.html	None
	Heart Line	Med/Heart/Heartline	None
	Heart Surgery Forum	www.hsforum.com	None
	JFP Journal Club	www.phypc.med.wayne.edu/jfp/jclub.htm	Under construction
	Internet Journal of Surgery	www.ispub.com/journals/ijs.htm	None
	Internet Journal of Thoracic and Cardiovascular Surgery	www.ispub.com/journals/ijtcvs.htm	None
	International Consortium for Alternative Academic Publication	www.ispub.com	None
Bio Sites www.library.usf.edu/biosites	Centerwatch Clinical Trials	www.centerwatch.com	None
	CTSnet	www.ctsnet.org	None
	Technology Online	www.ast.org	Inaccessible

CHAIN, Contact Help Advice Information Network; HSTAT, Health Services/Technology Assessment Text; FDA, US Food and Drug Administration; JFP, Journal of Family Practice*; CTSnet, Cardiothoracic Surgery Network; TRIP, Turning Research Into Practice; eBMJ,* electronic BMJ*; IDEA, Internet Database of Evidence-Based Abstracts and Articles; CCOHTA, Canadian Coordinating Office of Health Technology Assessment; ECRI, ; FINOHTA, Finnish Office for Health Technology Assessment; INAHTA, International Agency for Health Technology Assessment; NZHTA, New Zealand Health Technology Assessment; SBU, Statens Beredning für medicinsk Utvärdering (Swedish Council on Technology Assessment in Health Care)*

continued

TABLE 12 contd *Summary of Internet search results*

Gateway	Site	Address	Results
Medical Matrix www.medmatrix.org	Cardiovascular Medicine Module at Virginia	www.med.virginia.edu/%7Ersb2b/teaching/case	None
	Acuson	www.acuson.com/index2.html	None
	Cardiac Consultant	www.ccf.org/heartcenter/physinfor/cconsultant	None
	American Institute of Ultrasound in Medicine	www.aium.org	None
	Clinical Investigators	www.invantage.com	None
Bio Med Link www.biomednet.com/db/biomedlink	Centre for Evidence-Based Medicine	www.cebm.jr2.ox.ac.uk	None
Health on the Net www.hon.ch	Med 411	www.med411.com	None
	Cardiovascular Risk Factors (journal)	www.crf.medynet.com	None
	Cardiology Starting Point	www.geocities.com/SoHo/Bistro/3451	None
	British Cardiac Association	www.cardiac.org.uk	None
Hardin Meta Directory www.uiowa.edu/hardin/md/index.html	Med Web Plus	www.medwebplus.com	*Journal of Diagnostic Medical Sonography*
Health Web www.healthweb.org/	Electronic journals and newspapers	uky.edu/medicalcentre/medlibrary/ejournals.htm	Dead link
index.html	Heart Information Service	www.tmc.edu/thi/his.html	None
Internet Resources www.shef.ac.uk/~scharr/ir/netting.html	Guidelines	www.his.ox.ac.uk	None
	Centre for Clinical Effectiveness	www.med.monash.edu.au/publichealth/cce/	None
	Clinical Effectiveness Network in Dorset	www.cend.org.uk/index.htm	None
OMNI www.omni.ac.uk	TRIP	www.gwent.nhs.gov.uk/trip	None
	DARE	www.york.ac.uk	None
	eBMJ	www.bmj.com/cji/collector	None
	Guideline Research	www.mailbase.ac.uk/lists/guideline-research	None
	Clinical Evidence 99	www.bmjpg.com/evid99/index.html	New journal 1999
	AHA Scientific Publishing	www.amhrt.org/scientific/pubs/scipup/faq	None
	IDEA	www.ohsu.edu/bicc-informatics/ebm/ebm-topics	None
	Cardiology Today	www.slackinc.com/general/cardio/cardhom.htm	Two results: neither IVUS-guided interventions

CHAIN, Contact Help Advice Information Network; HSTAT, Health Services/Technology Assessment Text; FDA, US Food and Drug Administration; JFP, Journal of Family Practice*; CTSnet, Cardiothoracic Surgery Network; TRIP, Turning Research Into Practice; eBMJ, electronic* BMJ*; IDEA, Internet Database of Evidence-Based Abstracts and Articles; CCOHTA, Canadian Coordinating Office of Health Technology Assessment; ECRI, ; FINOHTA, Finnish Office for Health Technology Assessment; INAHTA, International Agency for Health Technology Assessment; NZHTA, New Zealand Health Technology Assessment; SBU, Statens Beredning für medicinsk Utvärdering (Swedish Council on Technology Assessment in Health Care)*

continued

TABLE 12 contd *Summary of Internet search results*

Gateway	Site	Address	Results
National Research Register www.doh.gov.uk/nrr.htm	National Research Register	www.doh.gov.uk/nrr.htm	13 results: 2, this review; 7, not IVUS-guided; 1, not coronary arteries
University of York, HNS CRD www.york.ac.uk	NHS Economic Evaluations Database	www.york.ac.uk	None
Copernic (HealthWeb Pages) www.herts.ac.uk/subject/health3.hlthwww.htm	Diagnostic Ultrasound Consultants	www.memphis.accessus.net/~dusc/	None
Copernic www.copernic.com	CCOHTA	www.ccohta.ca	None
	ECRI	www.ecri.org	None
	FINOHTA	www.ccohta.ca/main-e.html	Under construction
	INAHTA	www.ccohta.ca/main-e.html	None
	NCCHTA	www.ccohta.ca/main-e.html	None
	NZHTA	nzhta.chmeds.ac.nz	None
	SBU	www.ccohta.ca/main-e.html	None
	Agency for Healthcare Policy and Research	www.ccohta.ca/main-e.html	None
	Health News	www.mhs-nepa.com/news/2-11-b.html	None
	MedExpert	www.medexpert.net	None
	Cardiovascular *WWW* sites	www.mmip.mcgill.ca/heart/major.html	None
	Ultrasound Imaging (Sonography)	www.imaginiscoro.com/ultrasound	None
	Cardiac and other Medical Links	www.angelfire.com/or/CardiacLinks/index.html	None
	Evidence Based Medicine	www.medlib.iupui.edu	

CHAIN, Contact Help Advice Information Network; HSTAT, Health Services/Technology Assessment Text; FDA, US Food and Drug Administration; JFP, Journal of Family Practice*; CTSnet, Cardiothoracic Surgery Network; TRIP, Turning Research Into Practice; eBMJ, electronic* BMJ*; IDEA, Internet Database of Evidence-Based Abstracts and Articles; CCOHTA, Canadian Coordinating Office of Health Technology Assessment; ECRI, ; FINOHTA, Finnish Office for Health Technology Assessment; INAHTA, International Agency for Health Technology Assessment; NZHTA, New Zealand Health Technology Assessment; SBU, Statens Beredning für medicinsk Utvärdering (Swedish Council on Technology Assessment in Health Care)*

unique articles were found. In the MEDLINE search, 9973 RCTs were limited to 34 meta-analyses, of which 31 were in English. Of these, one was applicable to stenting but not in the coronary arteries. A review[111] was found from the DEC website and a report[112] on a meta-analysis acquired at an International Society for Technology Assessment in Health Care conference. Six[106–109,111,112] of the seven articles were available and included a total of 27 primary controlled trials that related to coronary stenting.

Additional topics

In-stent restenosis

Using the in-stent restenosis search strategy, 165 articles were retrieved within Reference Manager. Four articles were identified by handsearching in other parts of the review but were subsequently excluded, as they did not discuss the use of IVUS. A total of 124 articles were excluded on application of the exclusion criteria. Assessment showed that none of remaining 41 articles discussed the role of IVUS in planning the treatment of in-stent restenosis.

TABLE 13 *Journals (18 titles) identified by handsearching reference lists of all retrieved articles that are not indexed or incompletely indexed elsewhere*

Journal	Notes
Medical Ultrasonics	Not on Ulrich or Publist
Thoraxcentre Journal	Not on Ulrich or Publist
Randomised Clinical Trials	Not on Ulrich or Publist
Virchow's Archives of Pathology, Anatomy and Histopathology	Indexed in MEDLINE, EMBASE and BIDS up to 1993
Medical Instrumentation	Indexed in EMBASE and BIDS up to 1988
Modern Concepts of Cardiovascular Disease	Indexed in EMBASE and BIDS up to 1991
Vascular Forum	Not on Ulrich or Publist
Bulletin of the Society of National Chirug	Not on Ulrich or Publist
Clinical Progress in Pacing and Electrophysiology	Not on Ulrich or Publist
Coronary	Not on Ulrich or Publist
Fortschritte Rontgenstrahlen	Not on Ulrich or Publist
Polski Przeglad Chirurgiczny	Polish, English and Russian summaries
Journal of Atherosclerosis Research	Not on Ulrich or Publist
Cardiology Digest	Not on Ulrich or Publist
Acta Radiologica Diagnostica	Not on Ulrich or Publist
American Journal of Medical Science	Not on Ulrich or Publist
Dynamic Cardiovascular Imaging	Not on Ulrich or Publist
Heart Disease and Stroke	Indexed in MEDLINE and EMBASE up to 1994 (Ceased)

Reproducibility

In all, 313 articles were retrieved with the reproducibility search strategy within Reference Manager. Of these, 271 were excluded on application of the exclusion criteria. A further 11 articles were identified by handsearching in other parts of the review. Assessment showed that 11 articles did not discuss reproducibility, leaving 32 articles for validity assessment prior to data extraction. Although translation was not performed for this topic, it was possible to include one article[113] written in Italian. In all, 17 articles were included in the review.[113–129]

Articles included in the review

IVUS-guided interventions

As outlined in chapter 3 and *Figure 1*, eight possible roles for IVUS-guided coronary interventions were of interest. These roles could apply to IVUS-guided PTCA, atherectomy or stenting. Included articles are described in a standard format: study, aims, location and period, context, study size, methods and follow-up/comparability.

IVUS-guided PTCA

Only one study[130] on IVUS-guided angioplasty was included; it also used pre-interventional IVUS (Branch 3). Another article[131] reported IVUS-guided angioplasty but investigated its use with spot stenting and ROTA, rather than on its own, so was excluded.

Haase, *et al.*, 1998[130]

Aims To evaluate the safety, efficacy and long-term (12 months) post-intervention outcome of vessel size adapted PTCA of patients with native coronary artery obstructions.

Location and period Tübingen, Germany: January–December 1995.

Context Although IVUS can be reliably used to measure the external elastic membrane (EEM) at the lesion site and, subsequently, size the balloon diameter, this study set out to determine whether this leads to a reduction in restenosis rate or to additional vascular complications.

Size 144 patients (152 lesions).

Methods This was a prospective, non-randomised, single-centre trial.

- Pre- and post-interventional IVUS: all measurements performed by one individual blinded to angiographic results.
- Satisfactory PTCA defined as a luminal CSA gain of at least 20% compared with the EEM

TABLE 14 *Journals, periodicals or series (23 titles) identified from Ulrich, Publist, and the Internet that are not indexed or incompletely indexed elsewhere*

Journal/periodical/series	Notes
Searched	
Journal of Diagnostic Medical Sonographers	Searched online
Core journals in cardiology	Covers five top medical journals, all individually searched
Ceased publication before start-date of review, or not relevant to topics of review	
Basic And Clinical Cardiology series	Irregular series, latest – volume 11, 1988
Cardiology update	Subtitled *Reviews for physicians*. Irregular book series; latest, 1990
Current Status Of Clinical Cardiology	Series; volume 1, 1990, applicable
Diagnostic Cardiology	Quarterly, 1989–91 (now ceased)
Echocardiography Journal of Cardiac Ultrasound	Biweekly available online (www2.umdnj.edu/~schindler); clinical trials and images
Interventional Cardiology	Irregular, 1991; monograph series. Volume 1 published, not on IVUS
Interventional Cardiology Newsletter	Bimonthly newsletter, 1993
Newspaper of Cardiology	Monthly
Recent advances in cardiology	Book, edited by DJ Rowlands; 1996
Possibly relevant, but not followed-up	
Cardio Intervention	Quarterly;1991
Cardiology in Practice	Monthly
Current Diagnosis and Treatment in Cardiology	Irregular
Current Review of Interventional Cardiology	Irregular monograph series; 1994
Current Medical Literature: Cardiology	Quarterly
Current Topics in Cardiology	Irregular; latest volume 3, 1992
Developments in Cardiology	Monthly
Interventional Cardiology Monitor	Quarterly; 1994
Journal of Interventional Cardiology	Bimonthly; 1988
New Clinical Applications: Cardiology	Irregular
Perspectives in Cardiology	10 issues per year
Technology for Cardiology	Monthly

CSA, and/or ultrasonic evidence of a dissection creating a second lumen with an angiographically patent flow to the distal vessel segment that persisted 20 minutes after PTCA.
- Concentrated on *de-novo* lesions and excluded AMI, left main stem lesions, total occlusions, type C lesions and vessel diameters < 2.0 mm.

Follow-up/comparability As pre-interventional IVUS could not be completed with sufficient quality, 27 patients were excluded. Angiographic follow-up rate was only 75%, with no explanation given. Study represents a population selected by their symptoms, with no control arm. The absolute angiographic restenosis rate of 21% should be interpreted with caution. The 16% clinical event rate (repeat PTCA, CABG, Q-wave MI or death) is from a well-defined, homogeneous study population.

IVUS-guided atherectomy

No full articles on IVUS-guided atherectomy were found. A candidate article in Japanese[101] did not appear to satisfy the inclusion criteria from inspection of the untranslated article. As it was not on a topic (stenting or PTCA) identified as a priority for translation it was not translated to confirm this.

IVUS-guided stenting

No evidence was found for Branches 2, 4 and 5 (*Figure 1*). These correspond to the use of pre-interventional IVUS with (Branch 2) and without (Branch 4) an adjunct technology and without IVUS guidance for stenting. For Branch 5, there is no pre-interventional IVUS but adjunct technologies are used before IVUS-guided stenting. No evidence was sought for Branch 6 as no evidence had been found for

TABLE 15 *Included studies for branch 1: patient characteristics*

Patient characteristic	Hoffman, *et al.*, 1998[132]	Kornowski, *et al.*, 1998[133]	Mudra, *et al.*, 1997[134]
Total number of patients	291	1790	80
Number of patients followed	291	1771	68
Male, %	76	71	85
Mean age, years	61.7 ± 10.9	Not reported	61 ± 15
Unstable (%)	84 (29)	1217 (68)	Not reported
CCS grade 0 (%)[a]	Not reported	Not reported	Not reported
CCS grade I (%)[a]	Not reported	Not reported	13 (19)
CCS grade II (%)[a]	Not reported	Not reported	12 (18)
CCS grade III (%)[a]	Not reported	Not reported	18 (26)
CCS grade IV (%)[a]	Not reported	Not reported	25 (37)
Previous MI (%)	204 (70)	931 (52)	31 (46)
Previous CABG (%)	204 (70)	788 (44)	Not reported
Previous PTCA (%)	Not reported	895 (50)	Not reported
Single vessel (%)	Not reported	Not reported	14 (21)
Diabetes (%)	56 (19)	448 (25)	Not reported
Smoker (%)	Not reported	Not reported	Not reported
Hypercholesterol (%)	253 (87)	1235 (69)	Not reported
Hypertension (%)	207 (71)	1056 (59)	Not reported
Family history (%)	Not reported	Not reported	Not reported
Mean number of stents per patient	1.6	Not reported	1.3

[a] *See appendix 1 for definition of CCS grades*

the comparator (Branch 5). Branch 8 corresponds with the control arm of our review, described later in this chapter.

There were 15 articles that satisfied the inclusion criteria. These are summarised below, organised by the role in which IVUS was used: Branch 1 (pre-interventional IVUS with an adjunct technology and with IVUS guidance for stenting), three articles; Branch 3 (pre-interventional IVUS with no adjunct technology and with IVUS guidance for stenting), three articles; Branch 7 (no pre-interventional IVUS with no adjunct technology and with IVUS guidance for stenting), ten articles. Three tables giving patient characteristics, lesion characteristics and study details accompany each group.

Branch 1: pre-interventional IVUS, adjunct technologies and IVUS-guided stenting

Patient characteristics are summarised in *Table 15*, lesion characteristics in *Table 16* and study details in *Table 17*.[132–134]

Hoffman, *et al.*, 1998[32]

Aims To evaluate clinical, pre- and post-interventional quantitative coronary angiographic (QCA) and IVUS predictors of restenosis after Palmaz–Schatz stent deployment.

Location and period Washington, DC: no dates given.

Context Although predictors of restenosis had been identified for PTCA alone and after non-stent devices, this study set out to determine those for stent procedures.

Size 291 patients (382 lesions).

Methods Pre- and post-interventional IVUS. Included within this group were 42 atheroablative (debulking) procedures (13% of total).

- Satisfactory IVUS criteria, defined as a minimal lumen stent CSA of 80% of average of proximal and distal reference diameters

TABLE 16 *Included studies for branch 1: lesion characteristics*

Lesion characteristic	Hoffman, *et al.*, 1998[132]	Kornowski, *et al.*, 1998[133]	Mudra, *et al.*, 1997[134]
Total number of lesions	382	2493	84
Lesions followed-up	382	1673*	72
LAD (%)	84 (22)	673 (27)	23 (32)
LcX (%)	40 (10)	399 (16)	15 (21)
RCA (%)	94 (25)	798 (32)	15 (21)
LM (%)	14 (3.7)	0	0
Graft (%)	150 (39)	623 (25)	19 (26)
Restenosis (%)	Not reported	418 (25)*	29 (40)
Lesion Type A (%)[a]	Not reported	Not reported	9 (13)
Lesion Type B1 (%)[a]	Not reported	Not reported	Not reported separately
Type B 42 (58)	Lesion Type B2 (%)[a]	Not reported	Not reported
Lesion Type C (%)[a]	Not reported	Not reported	21 (29)
Ostial (%)	62 (16)	249 (10)	Not reported
Mean length (mm)	9.8 ± 6.3	Not reported	10.6 ± 6.2
Calcified (%)	Not reported	552 (33)*	Not reported
Eccentric (%)	Not reported	803 (48)*	Not reported
Occluded (%)	9 (2.4)	Not reported	Not reported
Bifurcations (%)	Not reported	Not reported	Not reported
Thrombus (%)	Not reported	100 (6.0)*	Not reported
Angulation (%)	Not reported	Not reported	Not reported
Tandem (%)	Not reported	Not reported	Not reported
Tortuous (%)	Not reported	Not reported	Not reported
Ulceration (%)	Not reported	201 (12)*	Not reported
LVEF	Not reported	Not reported	58 ± 11
Mean number of stents per lesion	1.2	Not reported	1.2

**Values only from those lesions followed-up*
[a] See appendix 1 for definition of types A, B1, B2 and C

(or absolute minimum of 7.5 mm^2 in native arteries or 9 mm^2 in vein grafts).
- No information given with regard to post-stent medication.
- High risk rating: group included atheroablative procedures, left main stem occlusions, as well as ostial and bifurcation lesions.

Follow-up/comparability There was potential for selection bias. Those undergoing follow-up may have been disproportionately selected by virtue of their symptomatic status. Authors argued this not to be the case, at least for pre-stent IVUS, because of the routine use at that centre. As with the paper by Kornowski and colleagues,[133] there was potential for operator bias in the choice of treatment as these initial images were not blinded. No definitive conclusion can be drawn about the 13% of patients who underwent atheroablative procedures.

Kornowski, *et al.*, 1997[133]
Aims To evaluate the procedural success, major complications and clinical outcomes after 1 year in a consecutive series of patients treated with multiple contiguous stents.

Location and period Washington, DC: January 1994–December 1995.

Context Performed in the historical context of stent development, particularly the restricted availability of stents in the USA. This restriction included a lack of relatively long stents, necessitating the alternate use of multiple stents in the eventuality of a long dissection or for long lesions.

TABLE 17 *Details of included studies: branch 1*

	Hoffman, *et al.*, 1998[132]	Kornowski, *et al.*, 1998[133]	Mudra, *et al.*, 1997[134]
Study period	Not reported	1/94–12/95	2/94–4/95
Centre	Washington Hospital Centre, Washington, DC, USA	Cardiology Research Foundation Angioplasty Database, Washington DC, USA	Klinikum Innenstadt, Munich, Germany
Controlled	No	No	No
Randomised	No	No	No
Matched	No	No	No
Observational	Yes	Yes	Yes
Start point	Follow-up	Consecutive	Successful
IVUS available (%)	100	91	100
Follow-up period	Mean: 5.5 ± 4.8 months	1 year	6 months
Angiography (%)	100	67	100
Clinical (%)	None	99	100
Aspirin alone	Not reported	No	65%
Aspirin + ticlopidine	Not reported	100%	35%
Other therapy	Not reported	Heparin	No

Although stent use had been validated within the confines of the relatively conservative entry criteria of the Benestent trial[33] and STRESS (Stent Restenosis Study)[34] studies, the benefits had not been proven for multiple stents.

Size A total of 117 consecutive patients with three or more stents were compared with the rest of a cohort of 1673 patients with either one or two stents.

Methods Retrospective study.

- IVUS criteria not stated but described as 'carefully monitored by an iterative technique with prespecified IVUS endpoints'.
- All patients received aspirin and ticlopidine. High-risk patients, including the group under analysis, were additionally treated with 2 weeks of low molecular weight heparin (LMWH).
- Both groups had in excess of 60% with unstable angina and thus represent a high-risk group.

Follow-up/comparability Patients were assessed who had undergone IVUS before stenting in 91% of cases, thus treatment may have been significantly influenced if compared with those studies in which IVUS was performed only after stent deployment. Lesion severity is, as a rule, underestimated when angiography is compared with IVUS and it is likely, therefore, that this study would have been biased to more extensive treatment for similar lesion appearances. For this reason, the study should ideally be compared only with similarly designed studies, such as that by Hoffman and colleagues.[132]

Mudra, *et al.*, 1997[134]

Aims To compare immediate and long-term angiographic and ultrasound measurements after IVUS-guided deployment in a consecutive series of patients.

Location and period Munich, Germany; February 1994–April 1995.

Size Study had no control arm and only a small number of patients – 85 in total with 84 lesions.

Methods Non-randomised study.

- IVUS criteria used were as for MUSIC (Multicenter Ultrasound Stenting In Coronaries) study[44] (see appendix 1). Of the 80 patients, 12 were excluded from analysis because of 'technical' shortcomings.
- Patients who successfully met IVUS criteria (44 patients) took aspirin only. Remaining 24 patients also took ticlopidine.
- Patients represent an unusual mix, with a very high proportion of restenotic lesions. Suggests bias towards indication for IVUS use rather than routine or unselected use.

TABLE 18 *Included studies for branch 3: patient characteristics*

Characteristic	Abizaid, *et al.*, 1998[135]	Hoffman, *et al.*, 1997[136]	Jeremias, *et al.*, 1999[137]
Total number of patients	954	71	42
Number of patients followed-up	954	71	42
Male (%)	72	75	90
Mean age (years)	Not reported	62 ± 11	58 ± 9
Unstable (%)	636 (67)	9 (13)	8 (19)
CCS grade 0 (%)[a]	Not reported	Not reported	Not reported
CCS grade I (%)[a]	Not reported	Not reported	6 (14)
CCS grade II (%)[a]	Not reported	Not reported	18 (43)
CCS grade III (%)[a]	Not reported	Not reported	13 (31)
CCS grade IV (%)[a]	Not reported	Not reported	5 (12)
Previous MI (%)	486 (51)	36 (51)	18 (12)
Previous CABG (%)	219 (23)	Not reported	Not reported
Previous PTCA (%)	500 (52)	Not reported	Not reported
Single vessel (%)	Not reported	Not reported	Not reported
Diabetes (%)	248 (26)	Not reported	2 (5)
Smoker (%)	467 (49)	Not reported	17 (40)
Hypercholesterol (%)	643 (67)	Not reported	35 (83)
Hypertension (%)	556 (58)	Not reported	28 (67)
Family history (%)	Not reported	Not reported	Not reported
Mean number of stents per patient	Not reported	1.20	1.52

[a] *See appendix 1 for definition of CCS grades*

Follow-up/comparability The study's lack of a control arm is further compounded in this instance by the appparent bias towards a high percentage with restenosis. The overall risk rating is moderate.

Branch 3: pre-interventional IVUS, no adjunct technologies and IVUS-guided stenting

Patient characteristics are summarised in *Table 18*, lesion characteristics in *Table 19* and study details in *Table 20*.[135–137] For Jeremias and colleagues,[137] the values in the tables refer only to the group receiving pre-intervention IVUS.

Abizaid, *et al.*, 1998[135]

Aim To compare the clinical outcomes of coronary artery stenting according to diabetic status.

Location and period Washington, DC; January 1994–January 1996.

Context Although it was known that diabetic patients had an increased rate of restenosis following PTCA, it was not known if this applied to stented lesions, nor if the risk was the same within the diabetic subgroups. The reason to hypothesise a difference was because two of the three components of restenosis following PTCA, namely vessel wall remodelling and elastic recoil, are nullified by the scaffolding structure provided by the stent. Neointimal hyperplasia is left as the sole contributor to restenosis in stented lesions.

Size Data for paper were taken from database, not from prospective study with planned recruitment of prespecified number of patients and a null and alternative hypothesis. Nonetheless, study was of reasonable size and statistical power was such that significant differences were observed between groups.

Methods

- IVUS measure of optimal stent deployment used was at least 80% of the averaged proximal and distal reference segments.
- All patients received aspirin and ticlopidine, with additional LMWH in high-risk patients.

TABLE 19 *Included studies for branch 3: lesion characteristics*

Lesion characteristic	Abizaid, et *al.*, 1998[135]	Hoffmann, et *al.*, 1997[136]	Jeremias, et *al.*, 1999[137]
Total number of lesions	1304	71	42
Number of lesions followed-up	1304	71	42
LAD (%)	404 (31)	13 (18)	26 (62)
LCx (%)	277 (21)	9 (13)	7 (17)
RCA (%)	592 (45)	20 (28)	9 (21)
LM (%)	31 (2.4)	4 (6)	0
Graft (%)	0	25 (35)	0
Restenosis (%)	Not reported	Not reported	Not reported
Lesion type A (%)[a]	Not reported	Not reported	Not reported
Lesion type B1 (%)[a]	Not reported	Not reported	Not reported
Lesion type B2 (%)[a]	Not reported	Not reported	Not reported
Lesion type C (%)[a]	Not reported	Not reported	Not reported
Ostial (%)	70 (5.4)	Not reported	Not reported
Mean length (mm)	Not reported	Not reported	10.8 ± 5.7
Calcified (%)	142 (11)	Not reported	Not reported
Eccentric (%)	683 (52)	Not reported	Not reported
Occluded (%)	Not reported	Not reported	Not reported
Bifurcations (%)	92 (7.1)	Not reported	Not reported
Thrombus (%)	36 (2.8)	Not reported	Not reported
Angulation (%)	Not reported	Not reported	Not reported
Tandem (%)	Not reported	Not reported	Not reported
Tortuous (%)	Not reported	Not reported	Not reported
Ulceration (%)	149 (11)	Not reported	Not reported
LVEF	Not reported	Not reported	Not reported
Mean number of stents per lesion	Not reported	1.20	1.5 ± 0.9

[a] *See appendix 1 for definition of lesion types A, B1, B2 and C*

- Cohort was 'consecutive' and, overall, would be considered a high-risk group for complications. Series had high proportion with unstable angina and did not exclude patients with thrombus, calcification, ostial or bifurcation lesions.

Follow-up/comparability No impartial objective measure, preferably angiographic, used. Preconceived notions of poorer outcome in diabetic patients may have introduced clinician bias and led to a lower threshold for both repeat angiography and further TLR. Equally seriously, study was fundamentally flawed by failure to match stented vessels according to diameter. EEM was significantly smaller for the insulin-dependent diabetes mellitus (IDDM) group and failure to control for this may have significantly contributed to the apparent differences in restenosis rates. Overall proportion of patients with diabetes in the cohort was 26% (IDDM 10.2%, non-insulin-dependent diabetes mellitus (NIDDM) 15.8%), approximately double that of the Milan cohort[138] of otherwise similar heterogeneity and risk.

Hoffman, *et al.*, 1997[136]

Aims To compare serial quantitative angiographic and IVUS studies in a consecutive series of patients treated with tubular slotted coronary stents.

Location and period Washington, DC; no dates given.

Size A total of 71 in a consecutive series of 231 patients.

TABLE 20 *Details of included studies: branch 3*

	Abizaid, *et al.*, 1998[135]	**Hoffmann, *et al.*, 1997[136]**	**Jeremias, *et al.*, 1999[137]**
Study period	1/94–1/96	Not reported	12/95–6/96
Centre	Cardiology Research Foundation, Angioplasty Database, Washington DC, USA	Washington Hospital Centre, Washington DC, USA	Essen, Germany
Controlled	No	No	No
Randomised	No	No	No
Matched	Yes	Yes	Yes
Observational	Yes	Yes	Yes
Start point	Consecutive	Consecutive	Consecutive
IVUS available (%)	94	100	Not reported
Follow-up period	1 year	Mean 5.5 ± 4.1 months	Mean 6 ± 2 months
Angiography (%)	N/A	100%	Not extractable from data presented
Clinical (%)	99.6	N/A	100
Aspirin alone	No	Not reported	No
Aspirin + ticlopidine	100%	Not reported	100%
Other	Heparin	Not reported	None

Methods
- Consecutive series; majority of patients disqualified because entry into study required the luminal dimension to be > 1 mm^2 for each and every IVUS measurement, in order that accurate IVUS measurements could be made.
- Palmaz–Schatz and biliary stents used.
- Operators not blinded to IVUS results.
- Target of > 80% of the average of proximal and distal reference CSAs by IVUS used for criteria of optimal stent deployment.

Follow-up/comparability Although study provides binary restenosis rates, the primary objective was to determine whether systematic errors occurred between the two methods; QCA and IVUS. Restenosis rates from this study are not easily comparable to other studies because of the necessary bias towards either relatively large vessels (over one-third were grafts) or relatively mildly stenosed lesions, in order that collection of IVUS data could be obtained. There were a high proportion of grafts but relatively few patients with unstable angina. Other baseline demographic data were not supplied.

Jeremias, *et al.*, 1999[137]
Size In total, 85 patients randomised to two groups.

Location and period Essen, Germany; December 1995–July 1996.

Methods A small study that appears to be greatly underpowered.

- Aspirin and ticlopidine for all patients.
- MUSIC[44] criteria (appendix 1) for optimal stent deployment.
- Balloon to artery ratio well matched.

Follow-up/comparability Information relating to follow-up was inadequate; no reasons were given for 16% of patients who did not undergo repeat angiography. Other than symptomatic status, no information was available to compare either baseline characteristics or procedural parameters. The number of diabetic patients in this population was relatively modest in comparison with other groups reviewed in this series of papers, as was the number of patients with unstable angina. They do not therefore fully represent the highest-risk group for restenosis, despite the relatively high restenosis rate observed.

Comment The well-matched balloon to artery ratio may well reflect the experience of the operators at this centre. However, in combination with the expected similar final lumen dimensions and percentages that achieved target criteria for optimal stent deployment, it was not surprising that final restenosis rates were statistically similar. The only logical difference in restenosis rate could have occurred as a result of another variable.

Branch 7: no pre-interventional IVUS, no adjunct technologies and IVUS-guided stenting

Patient characteristics are summarised in *Table 21*, lesion characteristics in *Table 22* and study details in *Table 23*.[44,105,115,137–143] Note that the data in the tables for Jeremias and colleagues[137] represent the subgroup receiving no pre-interventional IVUS. The data in the tables from Albiero and colleagues[138] represent the total study population who received IVUS-guided stenting, including patients who had undergone one of two different stenting protocols. In this review, only results from those undergoing the more recent protocol were included.

Albiero, *et al.*, 1996[138]

Aims To determine whether use of IVUS for final stent optimisation impacts on the initial lumen gain and reduces the risk of restenosis.

Location and period Milan, Italy; March 1993–November 1995. Hamburg, Germany; June 1994–November 1995.

Context An attempt to address the issue of whether optimal IVUS-guided stenting is superior to angiography-directed high-pressure stenting in both immediate and 6-month outcomes.

Size A total of 173 IVUS lesions (from a total of 445 eligible) were matched with 173 non-IVUS lesions (from a total of 476 eligible).

Methods A retrospective study from the Milan group.

- Between March and September 1993 (the early phase of the Milan experience), the target for defining IVUS success was the achievement of a stent lumen CSA of 60% of the average of the proximal and distal vessel CSAs (measured at the media). In this phase, non-compliant balloons sized close to the IVUS average distal vessel (media to media) were used. These balloons were oversized in relation to the angiographic vessel diameter by visual estimate and inflated at moderate to high pressure. In September 1993, the IVUS criterion for optimal stent expansion was changed (the late phase in Milan). The goal was to achieve a stent lumen CSA equal to, or greater than, the distal reference lumen CSA. Non-compliant balloons were selected with a calculated nominal CSA 25–30% larger than distal lumen CSA, and inflated at high pressure.
- Both centres treated 98% of their patients with antiplatelet regime of either aspirin alone or aspirin plus ticlopidine. The remaining 2% were treated with warfarin.
- Patients appear relatively well matched in their baseline characteristics other than for number of active smokers, number with hypercholesterolaemia and number of vessels diseased.

Follow-up/comparability An attempt was made to simulate something akin to a controlled trial by retrospectively matching lesions treated by two methods of interest. In this instance, a 'control' arm to the study was sought from another European centre that only used high-pressure deployment techniques without IVUS. These were matched against the IVUS-guided stent database. The study was fundamentally flawed by change in IVUS techniques that took place part of the way through, and would have been more valid if the Milan patients had been excluded prior to September 1993. With this exclusion, the patients would also have been more contemporaneous.

Blasini, *et al.*, 1998[139]

Aims To test the hypothesis that patients fulfilling IVUS criteria for optimal coronary stent deployment show a reduction in the 6-month restenosis rate.

Location and period Munich, Germany; March 1994–May 1995.

Context Prior studies had indicated that improvements in stent deployment could be achieved with IVUS guidance. It was unclear if this would translate into alterations in observed restenosis rates.

Size A total of 250 'consecutive' patients who had successfully undergone coronary stent placement were recruited from unknown total population undergoing coronary intervention.

Methods

- IVUS criteria used for optimal stent deployment included intrastent minimal lumen area of > 8 mm^2 and/or $> 90\%$ of the average of proximal and distal reference areas.
- Anticoagulation was randomised either to aspirin plus ticlopidine or to aspirin plus phenprocoumaron.
- Patient baseline characteristics appear to have been well matched other than for cigarette smoking status.
- Methodology open to a significant bias effect from failure to randomise procedure

TABLE 21 *Patient characteristics in included studies: branch 7*

	Albiero, *et al.*, 1997[138]	**Blasini, *et al.*, 1998**[139]	**Carrozza, *et al.*, 1998**[140]	**de Jaegere, *et al.*, 1998**[44]	**Fitzgerald, *et al.*, 1999**[105 a]	**Hall, *et al.*, 1996**[141]	**Jeremias, *et al.*, 1999**[137]	**Mudra, *et al.*, 1994**[115]	**Schiele, *et al.*, 1998**[142]	**Serruys, *et al.*, 1998**[143]
Total number of patients	158	125	49	161	270	226	85	20	79	165
Number followed-up	158	105	49	161	270	226	85	16	79	165
Male (%)	91	78	86	82	69	88	85	Not reported	86	78
Mean age ± SD (years)	58.5 ± 8.9	58.2 ± 10.5	59 ± 11	60 ± 10	60 ± 11	Not reported	Not reported	61 ± 10	57 ± 10	60 ± 10
Unstable (%)	35 (22)	44 (42)	Not reported	0	Not reported	45 (20)	16 (19)	Not reported	Not reported	77 (47)
CCS grade 0,[b] *n* (%)	Not reported	Not reported	5 (10)	11 (6.8)	22 (8)	14 (6.2)	Not reported	Not reported	20 (25)	8 (4.8)
CCS grade I,[b] *n* (%)	Not reported	Not reported	6 (12)	15 (9.3)	24 (9)	49 (22)	12 (14)	Not reported	30 (38)	4 (2.4)
CCS grade II,[b] *n* (%)	Not reported	Not reported	6 (12)	70 (43)	49 (18)	67 (30)	32 (38)	Not reported	19 (24)	38 (23)
CCS grade III,[b] *n* (%)	Not reported	Not reported	12 (24)	60 (37)	81 (30)	72 (32)	29 (34)	Not reported	7 (8.9)	35 (21)
CCS grade IV,[b] *n* (%)	Not reported	Not reported	20 (41)	5 (3.1)	97 (36)	24 (11)	12 (14)	Not reported	3 (3.8)	3 (1.8)
Previous MI, *n* (%)	73 (46)	37 (35)	25 (51)	41 (25)	86 (32)	111 (49)	37 (44)	31 (46)	54 (68)	37 (22)
Previous CABG, *n* (%)	16 (10)	Not reported	5 (10)	4 (2.5)	24 (9)	17 (7.5)	Not reported	Not reported	0	6 (3.6)
Previous PTCA, *n* (%)	14 (8.9)	22 (21)	8 (16)	14 (8.7)	Not reported	23 (10)	Not reported	Not reported	Not reported	19 (12)
Single vessel, *n* (%)	89 (56)	Not reported	Not reported	102 (63)	200 (74)	134 (59)	Not reported	20 (100)	Not reported	Not reported
Diabetes, *n* (%)	12 (7.6)	17 (16)	8 (16)	17 (11)	62 (23)	26 (12)	7 (8.2)	Not reported	9 (11)	25 (15)
Smoker, *n* (%)	63 (40)	45 (43)	17 (35)	97 (60)	78 (29)	140 (62)	30 (35)	Not reported	55 (70)	40 (24)
Hypercholesterol, *n* (%)	74 (47)	40 (38)	Not reported	68 (42)	Not reported	119 (53)	Not reported	Not reported	54 (68)	96 (58)
Dyslipidemia, *n* (%)	Not reported	Not reported	18 (37)	Not reported	105 (39)	Not reported	Not reported	Not reported	Not reported	Not reported
Hypertension, *n* (%)	58 (37)	55 (52)	27 (55)	70 (43)	140 (52)	91 (40)	61 (72)	Not reported	24 (30)	71 (43)
Family history, *n* (%)	64 (41)	Not reported	18 (37)	Not reported	Not reported	97 (43)	Not reported	Not reported	Not reported	67 (41)
Mean number of stents per patient	1.28	Not reported	1.14	1.18	Not reported	Not reported	1.42	1.0	1.0	Not reported

[a] *Results presented as percentages; number of patients therefore calculated*
[b] *See appendix 1 for definitions of CCS grades*

TABLE 22 *Lesion characteristics in included studies: branch 7*

	Albiero, *et al.*, 1997[138]	**Blasini, *et al.*, 1998**[139]	**Carrozza, *et al.*, 1998**[140]	**de Jaegere, *et al.*, 1998**[44]	**Fitzgerald, *et al.*, 1999**[105 a]	**Hall, *et al.*, 1996**[141]	**Jeremias, *et al.*, 1999**[137]	**Mudra, *et al.*, 1994**[115]	**Schiele, *et al.*, 1998**[142]	**Serruys, *et al.*, 1998**[143]
Total number of lesions	173	125	49	161	290	294	87	20	79	165
Number followed-up	173	105	49	161	290	294	87	16	79	165
LAD, *n* (%)	106 (61)	41 (39)	16 (33)	95 (59)	125 (43)	135 (46)	47 (54)	8 (50)	38 (48)	79 (48)
LcX, *n* (%)	17 (9.8)	18 (17)	12 (24)	20 (12)	70 (24)	57 (19)	15 (17)	0 (0)	9 (11)	30 (18)
RCA, *n* (%)	48 (28)	40 (38)	21 (43)	46 (29)	96 (33)	93 (32)	23 (26)	4 (25)	32 (41)	55 (33)
LM, *n* (%)	2 (1.2)	0	0	0	0	2 (0.7)	0	0	0	0
Graft, *n* (%)	0	6 (5.7)	0	0	0	4 (1.4)	0	4 (25)	0	0
Restenosis, *n* (%)	10 (5.8)	14 (13)	Not reported	0	Not reported	14 (4.8)	0	6 (30)	Not reported	0
Lesion type A, *n* (%)[a]	9 (5.2)	6 (5.7)	3 (6.1)	Not reported	23 (8)	29 (9.9)	Not reported	Not reported	5 (6.3)	9 (5.5)
Lesion type B1, *n* (%)[a]	78 (45)	12 (11)	11 (22)	Not reported	75 (26)	101 (34)	Not reported	Not reported	40 (51)	61 (37)
Lesion type B2, *n* (%)[a]	67 (39)	36 (34)	25 (51)	Not reported	165 (57)	114 (39)	Not reported	Not reported	27 (34)	94 (57)
Lesion type C, *n* (%)[a]	19 (11)	51 (49)	8 (16)	Not reported	26 (9)	55 (19)	Not reported	Not reported	7 (8.9)	0
Ostial, *n* (%)	Not reported	Not reported	Not reported	0	20 (7)	10 (3.4)	Not reported	Not reported	Not reported	0
Mean length ± SD (mm)	Not reported	Not reported	9.6 ± 4.0	< 15	11.2 ± 6.0	Not reported	Not reported	Not reported	7.7 ± 3.5	Not reported
Calcified, *n* (%)	25 (14)	Not reported	Not reported	Not reported	70 (24)	Not reported	Not reported	Not reported	Not reported	49 (30)
Eccentric, *n* (%)	Not reported	Not reported	22 (45)	Not reported	113 (39)	176 (60)	Not reported	Not reported	Not reported	138 (84)
Occluded, *n* (%)	11 (6.4)	19 (18)	Not reported	Not reported	3 (1)	33 (11)	Not reported	Not reported	0	Not reported
Bifurcations, *n* (%)	24 (14)	Not reported	Not reported	0	17 (6)	39 (13)	Not reported	Not reported	Not reported	Not reported
Thrombus, *n* (%)	2 (1.2)	Not reported	3 (6.1)	Not reported	15 (5)	13 (4.4)	Not reported	Not reported	Not reported	Not reported
Angulation (%)	Not reported	Not reported	36 ± 32°	Not reported	32° (11)	Not reported	Not reported	Not reported	Not reported	Not reported
Tandem, *n* (%)	Not reported	Not reported	Not reported	Not reported	Not reported	9 (3.1)	Not reported	Not reported	Not reported	0
Tortuous, n (%)	Not reported	Not reported	Not reported	0	9 (3)	Not reported	Not reported	Not reported	Not reported	Not reported
Mean LVEF ± SD	Not reported	Not reported	Not reported	Not reported	55 ± 10	Not reported	Not reported	Not reported	53 ± 13	Not reported
Mean number of stents per lesion ± SD	1.17 ± 0.44	Not reported	Not reported	1.18	1.4 ± 0.5	Not reported	1.39	1.0	1.0	Not reported

[a] *See appendix 1 for definitions of lesion types A, B1, B2 and C lesions*

TABLE 23 *Details of included studies: branch 7*

	Albiero, *et al.*, 1997[138]	**Blasini, *et al.*, 1998**[139]	**Carrozza, *et al.*, 1998**[140]	**de Jaegere, *et al.*, 1998**[44]	**Fitzgerald, *et al.*, 1999**[105 a]	**Hall, *et al.*, 1996**[141]	**Jeremias, *et al.*, 1999**[137]	**Mudra, *et al.*, 1994**[115]	**Schiele, *et al.*, 1998**[142]	**Serruys, *et al.*, 1998**[143]
Study period	3/93–9/95	3/94–9/94	8/95–5/96	2/95–9/95	4/96–5/97	1/94–3/95	11/95–7/96	Not reported	1/95–2/97	2/96–8/96
Centre	CCC	TUM	Multi	Multi	Multi	CCC	Essen	KI	Multi	Multi
Controlled	Yes	Yes	No	No	Yes	No	No	No	Yes	No
Randomised	No	No	No	No	No	No	No	No	Yes	No
Matched	Yes	Yes	No	No	No	No	No	No	No	No
Observational	No	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Start point	Follow-up angiography available	Successful stent	Consecutive	Consecutive	Acceptable image and follow-up	Successful IVUS-stent and random	Consecutive	Consecutive	Successful stent	Consecutive
IVUS available (%)	100	100	88	96	100	100	100	100	94	92
Follow-up time	6 months	186 days	12 months	6.6 ± 1.2 months	9 months	1 month	6 ± 2 months	5.2 ± 1.7 months	5–7 months	188 ± 44 days
Angiography (%)	100	85	N/A	92	N/A	N/A	87	88	93	90
Clinical (%)	100	N/A	88	100	100 (> 90)	100	100	100	100	100
Aspirin alone	Yes	No	No	Yes	Yes	54%	No	No	No	75%
Aspirin + ticlopidine	Yes	52/105	No	No	Yes	46%	Yes	No	100%	25%
Other	Anti-coagulation	Aspirin + heparin + phenpro-coumon	Heparin + warfarin	Aspirin + heparin + anti-coagulation	Aspirin + coumadin	None	No	Aspirin + coumadin	None	None

Centre: CCC, Centro Cuore Columbus, Milan, Italy; TUM, Technical University, Munich, Germany; KI, Klinikum Innenstadt, Munich, Germany

performed. This was potentially ameliorated by the temporal sequence used, with the IVUS cohort being recruited first. As a consequence, any learning curve experience would theoretically have been minimised. However, as suggested by the statistically significant higher balloon pressure and balloon to artery ratio, the operators' learning experience may have caused some overcompensation.

Follow-up/comparability Patients represented a higher-risk population. The major failing of the study arises from failure to randomise the procedures or to have performed documentary IVUS. Although 'to the best of their knowledge' there was no bias in treatment strategies between groups, the possibility remains that an evolution in the strategy of IVUS or non-IVUS guided stent groups could have occurred. Additionally, there is no confirmation that the operators were indeed the same. Interpretation of results is consequently difficult, particularly in view of statistical differences seen in balloon pressure and balloon to artery ratio. Other limitations included lack of information given on substantial number of patients who did not complete angiographic follow-up (16% of IVUS group and 14% of 'control' group). Although it was specified that these groups did not differ in their baseline characteristics, no comment was made on their clinical follow-up or reasons for not consenting to further angiography. Patients not consenting to further investigation may represent a group who had a worse experience periprocedurally. Information relating to differences in major clinical endpoints between consenters and non-consenters, or between the IVUS and non-IVUS groups, was also not given.

Carozza, *et al.*, 1998[140]
Aims To evaluate safety, feasibility, optimal deployment technique and 1-year clinical outcome for the Advanced Cardiovascular Systems Multilink® stent.

Location and period Boston, Massachusetts, Stanford University, California, Washington, DC, and Birmingham, Alabama; August 1995–May 1996.

Context The Advanced Cardiovascular Systems Multilink stent represented one of a 'second generation' of stents with improved flexibility while retaining radial strength.

Size A total of 49 'consecutive' patients from four different centres.

Methods Although not explicitly stated, criterion for IVUS optimisation appeared to be 70% of averaged proximal and distal reference vessel CSA. All patients received aspirin plus warfarin. Risk group was low to moderate, with exclusion of ACS being pertinent.

Follow-up/comparability Pilot study with restricted entry criteria, no control group, unexplained partial IVUS data (43/49) and no long-term angiographic follow-up. Clinical follow-up was also partial (43/49).

De Jaegere, *et al.*, 1998[44]
Aims To validate safety and feasibility of IVUS-guided stenting without subsequent anticoagulation and its impact on 6-month restenosis rate.

Location and period Multicentre; February–September 1995.

Context Conducted to assess the feasibility of improving both subacute thrombosis and restenosis rates; initiated by Colombo and colleagues, who had published an earlier related article.[144]

Size A total of 161 patients with no control group.

Methods
- IVUS criteria for stent optimisation were the best defined of any of the studies and have come to be the accepted benchmark. They are as follows:
  - complete apposition of stent over its entire length against the vessel wall
  - in-stent minimal lumen area at least 90% of average reference lumen area or at least 100% of lumen area of segment with lowest lumen area; in-stent lumen area of proximal stent entrance at least 90% of proximal reference lumen area; if in-stent lumen area > 9.0 mm^2, then in-stent minimal lumen area at least 80% of average reference lumen area or at least 90% of lumen area of reference segment with lowest lumen area
  - symmetrical stent expansion defined by ratio of minimum to maximum luminal diameter of at least 0.7.
- The medication used post stent deployment was based on achievement of satisfactory IVUS-defined deployment. Aspirin was given to patients with optimal deployment (80%) and aspirin plus ticlopidine to those with suboptimal deployment (20%).
- An open, multicentre, prospective registry. Overall risk would be considered low for this group of patients. Unstable angina was excluded

and there was a preponderance of Type A single *de-novo* lesions.

Follow-up/comparability There was a 92% angiographic follow-up, with explanations given for those not followed-up. However, study must be taken in the context that 15 centres participated with an average recruitment of only ten or so patients each. Patients were also low risk and antiplatelet therapy was not uniform, although biased against the more aggressive and routine use of both aspirin and ticlopidine. Comparability is severely compromised by lack of a control group of any form.

Fitzgerald, *et al.* [unpublished][105]
Aims To assess whether routine ultrasound guidance of coronary stent implantation improves clinical outcome compared with angiographic guidance alone in the high pressure stent deployment era.

Location and period Multicentre, USA; April 1996–May 1997.

Context Several studies had shown that IVUS could assess stent geometry more accurately than angiography and that a marker of clinical outcome was the degree of stent expansion. Additionally, use of IVUS had identified a significant proportion of stents that were underdeployed.

Size A total of 525 patients were enrolled as subset of the larger stent anti-thrombotic regimen study (STARS).[145] There were 229 patients in 'IVUS-documentary' group and 270 in the 'IVUS-guided' group.

Methods
- In all, 16 of 45 STARS[145] centres were chosen for their experience with IVUS.
- Fundamentally restricted by the necessity to avoid influencing primary randomisation of the STARS trial,[145] which was designed to compare three antithrombotic regimens (apirin alone, aspirin plus ticlopidine or aspirin plus warfarin). Thus, use of IVUS was assigned on a centre-by-centre basis. In the seven angiographic guidance centres, a blinded (documentary) IVUS examination was performed at end of procedure.
- No optimal stent criteria were designated.
- Patients appear to have been well matched other than for prevalence of multivessel disease and prior MI.

Follow-up/comparability Comparability has been critically affected by lack of any *a priori* criteria for optimal stent deployment within IVUS-guided centres. The only surrogate indication of initial failure to optimise is suggested by the 36% of patients requiring additional therapy. The ratio of three antithrombotic regimes according to group was not presented.

Comments Study was not truly randomised and the significance of statistical differences in prevalences of single- and multivessel disease, as well as prior MI, should not be ignored. There were no apparent differences between operator experience or centre workload.

Hall, *et al.*, 1996[141]
Aims Following the Milan group's earlier article[144] showing that it was safe to withhold anticoagulation after successful stent deployment, this study was set up to answer the question as to whether a benefit could be gained from the addition of ticlopidine to aspirin therapy.

Location and period Milan, Italy; January 1994–March 1995.

Size Of 226 patients, 103 were in the aspirin-alone arm and 123 in the aspirin plus ticlopidine arm. Although subacute thrombosis was one of the main outcomes of interest, and occurred infrequently, no attempt at a power calculation was made. Consequently, this was a grossly underpowered study.

Context Once preliminary studies had indicated that there was no clear catastrophic consequence of using either aspirin alone or in combination with ticlopidine, the issue as to whether there was any discernible difference between these two regimes needed to be resolved.

Methods Prospective, randomised, single-centre study.

- IVUS criteria were relaxed further from the Milan centre's previous stated targets. Here the satisfactory outcome was an intrastent lumen of 80% of distal reference vessel. If vessel was < 7.5 mm^2, the criterion was modified to require the stent luminal area to be greater than that of the distal lumen.
- Randomisation of therapy as above.
- Risk: high.

Follow-up/comparability Randomisation of this study was open label, and study was terminated prematurely following three deaths in the aspirin-alone group. No information was given about

restenosis rates and the study was insufficiently powered to comment on subacute thrombosis with any certainty.

Jeremias, *et al.*, 1999[137]
Summarised earlier (see page 37).

Mudra, *et al.*, 1994[115]
Aims To combine use of a balloon catheter with an integrated IVUS facility for stent deployment and guidance in order to improve acute lumen gain without procedural prolongation.

Location and period Munich, Germany; period not specified.

Size Twenty patients.

Context It was hypothesised that an integrated device might reduce risks of passing an IVUS catheter through a dilated stent as well as leading to shorter procedural times.

Methods
- Optimal stent deployment defined as achievement of 90% of the average reference CSA.
- Patients received aspirin plus warfarin.
- Patient risk group unclear: no baseline demographic information provided.

Follow-up/comparability Descriptive account suggesting feasibility of such a device. No useful assessment of safety or restenosis rates can be made with such a small underpowered study with no comparative arm. However, even without baseline demographics of these patients, it can be seen that procedures were performed in low-pressure inflation era. The interesting information is that a figure is given for both additional procedural and fluoroscopy time. Unfortunately, once again no comparison was made with a conventional IVUS catheter.

Schiele, *et al.*, 1998[142]
Aims To investigate impact of IVUS-guided stent deployment on 6-month restenosis rate.

Location and period France; January 1995–February 1997.

Context Although the use of stents had been shown to reduce restenosis, the impact of an additional immediate lumen gain (by IVUS guidance) over and above that achieved by high-pressure deployment alone had not been supported by a randomised trial.

Size Underpowered study: statistical calculation based on an unqualified link to cost expenditure and an over-ambitious projected reduction in restenosis.

Methods Multicentred, randomised, single-blinded study. Randomisation occurred **after** successful stent deployment by angiographic criteria.

- Chosen ultrasound criterion was a stent CSA of 80% of the averaged proximal and distal reference lumen.
- Ticlopidine plus aspirin for all patients.
- Low-risk patient group.

Follow-up/comparability Aside from large discrepancy between on- and off-line analysis, IVUS follow-up was available for 137/144 patients who underwent further angiography at 6 months. However, the study was underpowered and in a relatively low-risk patient group.

Serruys, *et al.*, 1998[143]
Aims To assess the use of aspirin alone following successful implantation of a Multilink stent as defined by on-line quantitative coronary angiography and IVUS, thus attempting to duplicate the result obtained in MUSIC[44] study.

Location and period Multicentre (18); March–August 1996.

Context Following on from the West European stent trial (WEST) I,[146] the Advanced Cardiovascular Systems Multilink stent was implanted in 100 patients; the study was designed to emulate the MUSIC[44] study in its rationale of avoidance of all drug therapy other than aspirin, unless suboptimal stent deployment was observed.

Size A total of 165 patients with no control group. The 18 centres averaged only nine patients each. There was an inference that the MUSIC[44] study was used as surrogate control group for comparison, despite difference in exclusion criteria.

Methods Prospective non-controlled study.
- MUSIC[44] study criteria were adopted (see appendix 1).
- Aspirin alone was given to 75% of patients. Aspirin plus ticlopidine were given to the remaining patients.
- Group were higher risk than in the MUSIC[44] study but, overall, represented moderate risk in view of entry criteria of single *de-novo* lesions despite high prevalence of unstable angina.

Follow-up/comparability Can be compared with MUSIC[44] study within limits – both were series with single *de-novo* lesions and neither had a true control arm. More complications would have been predicted with this study because of the higher proportion of patients with unstable angina.

Control arm articles

Four[105,138,139,142] of the ten articles included for their information on IVUS-guided stenting also provided information on stenting without IVUS guidance.

Of the 27 primary RCTs identified from the search for articles on PTCA with or without the addition of coronary stenting, five controlled trials of stenting versus PTCA[33,34,147,148,149] satisfied the inclusion criteria for relevance and validity. The findings of these studies are summarised in *Table 24*.

TABLE 24 *RCTs of PTCA vs. PTCA plus coronary stent placement*

Study	Patient characteristics	Numbers randomised/ type of analysis	Primary & secondary endpoints (follow-up point)	Results	Comments
Fischman, *et al.*, 1994[34] (STRESS study)	Symptomatic ischaemic heart disease Angiographic evidence of at least 70% stenosis Length of lesion < 15 mm Vessel diameter > 3 mm Exclusions: MI in previous week; contradictions to anticoagulation or anti-platelet agents; multiple lesions: ostial lesions; tortuosity of vessels Age: 60 ± 10 years Women: 17% stent; 27% PTCA Previous MI: 36%	PTCA: *n* = 203 Stent: *n* = 207 ITT	Primary: angiographic evidence of restenosis (defined as ≥ 50% restenosis at follow-up) Secondary: Death, MI, CABG, or repeat PTCA within 6 months of original procedure (6 months)	Restenosis rate: 42.5% PTCA vs. 31.6% stent (p = 0.046) Any event: 23.8% PTCA vs. 19.5% (p = 0.16)	Higher follow-up angiography rate in stent group (92% vs. 83%). This may bias result by inflating restenosis rate in PTCA group No evidence of effect of stent on major cardiac events or survival Palmaz–Schatz stent
George, *et al.*, 1998[147] (Follow-up study to Fischman, *et al.*[34])	Same study group as for Fischman, *et al.*[34]	As for Fischman, *et al.*[34]	Primary: death, MI, CABG, repeat PTCA Secondary: angina within (on average) 1 year of original procedure (1 year)	1 year outcomes: free from events 68.8% PTCA vs. 75.1% stent; 84% free of angina in both groups	No difference in angina status found Differences in event rates not significant if non-target lesion revascularisations removed
Macaya, *et al.*, 1996[148] (Follow-up study to Serruys, *et al.*[33])	Same study group as for Serruys, *et al.*[33]	As for Serruys, *et al.*[33]	Primary: death, CVA, MI, CABG, repeat PTCA, restenosis Secondary: angina (1 year)	1 year outcomes: free from events 68.5% PTCA vs. 76.8% stent (p < 0.04)	If revascularisations removed, no significant differences between PTCA and stent groups in event rates
Savage, *et al.*, 1998[149] (Follow-up study to Fischman, *et al.*[34])	Single new lesion in native arteries 410 from earlier study plus 188 new patients Exclusions: vessel diameter ± 3.0 mm	PTCA: *n* = 168 Stent: *n* = 163	Primary: death, MI, CABG, repeat PTCA Secondary: angiographic evidence of restenosis (defined as ≥ 50% restenosis at follow-up) (1 year)	1 year outcomes: free from events 67.3% PTCA vs. 77.9% stent (p = 0.019) Restenosis rate: 55% PTCA vs. 34% stent	Revascularisation accounts for difference in composite endpoints Angiographic follow-up in 84% overall. Loss to follow up may bias result Palmaz–Schatz stent
Serruys, *et al.*, 1994[33] (Benestent I study)	Stable angina Single new lesion in coronary artery Lesion < 15 mm long Vessel diameter ≥ 3 mm Exclusions: contradictions to anticoagulation or anti-platelet agents; ostial and bifurcation lesions Age: 58 ± 10 years Women: 20% Previous MI: 20%	PTCA: *n* = 258 Stent: *n* = 262	Primary: death, CVA, MI, CABG, repeat PTCA Secondary: restenosis rate at 6 months (6 months)	In hospital: composite primary endpoints 6.2% PTCA vs. 6.9% stent; RR (95% CI): 1.12 (0.58 to 2.14) At 6 months: composite primary endpoints 30% PTCA vs. 20% stent; RR (95% CI) 0.68 (0.50 to 0.92) Restenosis rate 32% PTCA vs. 22% stent	Less restenosis in stent group at 6 months follow-up Revascularisation accounts for difference in composite endpoints Palmaz–Schatz stent

Patient characteristics are summarised in *Table 25,* lesion characteristics in *Table 26* and study details in *Table 27*. Note that the data in these tables from Albiero and colleaues[138] represent the total study population who underwent stenting without IVUS guidance, including patients who had undergone one of two different stenting protocols. In this review, only results from those undergoing the more recent protocol were included.

Additional topics

In-stent restenosis articles

There were no articles in which the use of IVUS to guide treatment choice in in-stent restenosis was addressed.

Reproducibility articles

Intra-observer reproducibility It was intended to exclude articles in which the intra-observer comparison was between measurements made on the same image (thus not measuring the consistency of image interpretation for repeated imaging) and in which measurements were made only on diseased segments.

However, comparisons made in this way were reported in many articles, so their results have been included here separately. The articles[114,115] that satisfied all the inclusion criteria are listed in *Table 28*; those[113,116–127] that used the same image twice or used only diseased segments but otherwise satisfied the inclusion criteria are listed in *Table 29*.

In the columns labelled diameter and area, the values presented are, in the main, the mean difference between paired measurements, plus or minus the SD of the mean difference. When the value is expressed as a percentage, the authors have calculated each difference as a fraction of one of the pair or of their mean value, before finding the mean percentage difference. It is not possible to convert between the methods of presentation without the original raw data. One article has been widely quoted;[120] however, the results were presented graphically and could not be obtained from the authors in numerical form.

Inter-observer reproducibility A total of 15 articles[113–114,116–125,127–129] were included in the review. Their results are summarised in *Table 30*.

Health economics articles

No health economics articles were included in the review.

Decision-analytic model

The intervention chosen as the focus for the decision model was stenting, as it was the one for which most evidence was available.

Data from the literature

Three[44,137,143] of the ten[105,138–143] included articles on IVUS-guided stenting, without pre-interventional IVUS or adjunct technology, supplied information in a form that fitted the decision tree (*Figure 2*). These were observational studies following a total of 365 patients. The 6-month outcome findings are summarised in *Tables 31* and *32*. The total MACE rate within the 6-month period was 43 in 37 patients: one death; four Q-wave MIs; six non-Q-wave MIs; three CABGs; 24 repeat PTCAs; and five undefined events. The figures shown in the MACE column of the table represent only one event (the worst) for each patient. It was not necessary to estimate the numbers having repeat PTCA or CABG, as sufficient data were provided in the articles.

Two[33,34] of the nine included articles[105,138,139,142,147–149] on non-IVUS-guided stenting supplied information on both the clinical and angiographic follow-up in a form that fitted the decision tree (*Figure 2*). The articles were RCTs of stenting versus PTCA and followed a total of 454 patients who had received stents. The 6-month outcome findings are summarised in *Tables 33* and *34*. The total MACE rate within the 6-month period was 105 in 84 patients: five deaths; 24 MIs; 18 CABGs and 58 repeat PTCAs. In neither article were the results split between angiographic and clinical outcomes, nor was there a breakdown of the numbers proceeding to repeat PTCA and CABG. The numbers were estimated, assuming that the proportion of each type was the same as in the corresponding part of the IVUS-guidance branch.

Probabilities derived from the values in *Tables 31–34* are given on the decision tree in *Figure 3*, together with the 95% CIs.

From McKenna and colleagues[77] updated to 1998, the cost was £3200 for a repeat PTCA, £5600 for an emergency CABG and £6000 for an elective CABG.

Empirical economics data

The procedural details and the time spent in the catheterisation laboratory for the IVUS-guided stenting and the non-IVUS guided stenting patients are recorded in *Tables 35* and *36*, respectively.

TABLE 25 *Patient characteristics in included articles: control arm*

	Albiero, *et al.*, 1997[138]	**Blasini, *et al.*, 1998**[139]	**Fischman, *et al.*, 1994**[34]	**Fitzgerald, *et al.*, 1999**[105]	**George, *et al.*, 1998**[147]	**Macaya, *et al.*, 1996**[148]	**Savage, *et al.*, 1998**[149]	**Schiele, *et al.*, 1998**[142]	**Serruys, *et al.*, 1994**[33]
Total number of patients	154	125	207	229	207	262	163	76	262
Number of patients followed	154	107	205	229	205	258	163	73	259
Males (%)	88	77	83	72	83	80	74	93	80
Mean age ± SD (years)	58.1 ± 10	59.9 ± 11.1	60 ± 10	61 ± 11	60 ± 10	57 ± 9	59 ± 10	56 ± 12	57 ± 9
Number unstable (%)	33 (21)	46 (43)	96 (47)	Not reported	96 (47)	Not reported	91 (56)	Not reported	Not reported
CCS grade 0[a] (%)	Not reported	Not reported	Not reported	11 (5)	Not reported	27 (10)	Not reported	24 (32)	27 (10)
CCS grade I[a] (%)	Not reported	Not reported	Not reported	16 (7)	Not reported	9 (3)	Not reported	25 (33)	9 (3)
CCS grade II[a] (%)	Not reported	Not reported	Not reported	48 (21)	Not reported	82 (32)	Not reported	21 (28)	82 (32)
CCS grade III[a] (%)	Not reported	Not reported	Not reported	73 (32)	Not reported	125 (48)	Not reported	5 (6.6)	125 (48)
CCS grade IV[a] (%)	Not reported	Not reported	Not reported	80 (35)	Not reported	16 (6)	Not reported	1 (1.3)	16 (6)
Previous MI (%)	65 (42)	40 (37)	76 (37)	94 (41)	76 (37)	52 (20)	Not reported	48 (63)	52 (20)
Previous CABG (%)	8 (5.2)	Not reported	Not reported	16 (7)	8 (4)	0	Not reported	Not reported	0
Previous PTCA (%)	16 (10)	19 (18)	Not reported	Not reported	21 (10)	5 (2)	Not reported	Not reported	5 (2)
Single vessel (%)	73 (47)	22 (21)	131 (64)	128 (56)	131 (64)	Not reported	Not reported	76 (100)	Not reported
Diabetes (%)	10 (6.5)	15 (14)	31 (15)	41 (18)	31 (15)	17 (7)	28 (17)	8 (11)	17 (7)
Smoker (%)	39 (25)	57 (53)	43 (21)	60 (26)	43 (21)	62 (24)	41 (25)	51 (67)	62 (24)
Hypercholesterol (%)	123 (80)	35 (33)	90 (44)	76 (33)	90 (44)	89 (34)	Not reported	52 (68)	89 (34)
Hypertension (%)	85 (55)	53 (50)	88 (43)	135 (59)	88 (43)	80 (31)	88 (54)	26 (34)	80 (31)
Family history (%)	58 (38)	Not reported	76 (37)	Not reported	Not reported	Not reported	Not reported	Not reported	160 (39)
Mean number of stents per patient	1.18	Not reported	1.0	Not reported	1.0	1.0	1.0	Not reported	1.0

[a] *See appendix 1 for definition of CCS grades*

TABLE 26 *Lesion characteristics in included articles: control arm*

	Albiero, et *al.*, 1997[138]	**Blasini, et *al.*, 1998**[139]	**Fischman, et *al.*, 1994**[34]	**Fitzgerald, et *al.*, 1999**[105]	**George, et *al.*, 1998**[147]	**Macaya, et *al.*, 1996**[148]	**Savage, et *al.*, 1998**[149]	**Schiele, et *al.*, 1998**[142]	**Serruys, et *al.*, 1994**[33]
Total number of lesions	173	125	207	253	205	262	163	76	262
Number followed-up	173	107	205	253	205	259	163	73	259
LAD (%)	106 (61)	42 (39)	96 (47)	116 (46)	96 (47)	165 (64)	96 (59)	36 (47)	165 (64)
LCx (%)	17 (9.8)	17 (16)	33 (16)	46 (18)	33 (16)	34 (13)	23 (14)	8 (11)	34 (13)
RCA (%)	48 (28)	42 (39)	76 (37)	91 (36)	76 (37)	60 (23)	44 (27)	32 (42)	60 (23)
LM (%)	2 (1.2)	0	0	0	0	0	0	0	0
Graft (%)	0	6 (5.6)	0	0	0	0	0	0	0
Restenosis (%)	15 (8.7)	13 (12)	0	Not reported	0	0	0	Not reported	0
Lesion type A (%)[a]	18 (10)	4 (3.7)	Not reported	25 (10)	41 (20)	Not reported	Not reported	8 (11)	Not reported
Lesion type B1 (%)[a]	57 (33)	8 (7.5)	Not reported	53 (21)	76 (37)	Not reported	Not reported	31 (41)	Not reported
Lesion type B2 (%)[a]	76 (44)	39 (36)	Not reported	152 (60)	84 (41)	Not reported	Not reported	26 (34)	Not reported
Lesion type C (%)[a]	22 (13)	56 (52)	Not reported	23 (9)	2 (1)	Not reported	Not reported	11 (14)	Not reported
Ostial (%)	Not reported	Not reported	0	15 (6)	0	0	Not reported	Not reported	0
Mean length ± SD (mm)	Not reported	Not reported	9.6 ± 3.0	10.6 ± 6.0	9.6 ± 3.0	7.06 ± 2.56	8.9 ± 3.0	8.05 ± 4.05	7.06 ± 2.56
Calcified (%)	11 (6.4)	Not reported	35 (17)	53 (21)	35 (17)	29 (11)	28 (17)	Not reported	29 (11)
Eccentric (%)	Not reported	Not reported	135 (66)	109 (43)	135 (66)	Not reported	95 (58)	Not reported	Not reported
Concentric (%)	Not reported	Not reported	Not reported	Not reported	Not reported	130 (50)	Not reported	Not reported	130 (50)
Occluded (%)	11 (6.4)	17 (16)	Not reported	Not reported	Not reported	9 (3)	Not reported	0	9 (3)
Bifurcations (%)	13 (7.5)	Not reported	Not reported	20 (8)	Not reported	0	5 (3)	Not reported	0
Thrombus (%)	4 (2.3)	Not reported	4 (2)	5 (2)	Not reported	0	11 (7)	Not reported	0
Angulation (%)	Not reported	Not reported	27 (13)	30 (12)	Not reported	Not reported	Not reported	Not reported	Not reported
Tandem (%)	Not reported	Not reported	Not reported	Not reported	Not reported	1	Not reported	Not reported	1
Tortuous (%)	Not reported	Not reported	0	15 (6)	0	Not reported	Not reported	Not reported	Not reported
LVEF ± SD	66.2 ± 11.1	Not reported	61 ± 12	Not reported	61 ± 12	Not reported	Not reported	51 ± 9	Not reported
Mean number of stents per lesion ± SD	1.05 ± 0.46	Not reported	1.0	1.4 ± 0.6	1.0	1.0	1.0	1.0	1.0

[a] *See appendix 1 for definition of lesion types A, B1, B2 and C*

TABLE 27 *Details of included studies: control arm*

	Albiero, *et al.*, 1997[138]	**Blasini, *et al.*, 1998**[139]	**Fischman, *et al.*, 1994**[34]	**Fitzgerald, *et al.*, 1999**[105]	**George, *et al.*, 1998**[147]	**Macaya, *et al.*, 1996**[148]	**Savage, *et al.*, 1998**[149]	**Schiele, *et al.*, 1998**[142]	**Serruys, *et al.*, 1994**[33]
Study period	6/94–11/95	10/94–5/95	1/91–2/93	4/96–5/97	1/91–2/93	2/96–8/96	1/91–2/93	1/95–2/97	6/91–3/93
Centre	CCO	TUM	Multi	Multi	Multi	Multi	Multi	Multi	Multi
Start point	Follow up angiography available	Successful stent	Consecutive	Acceptable + follow-up	Consecutive	Consecutive	Substudy within STRESS[34]	Successful stent	Consecutive
Follow-up time	6 months	6 months	6 months	9 months	1 year	1 year	1 year	6 months	6 months
Angiography (%)	100	86	86	N/A	N/A	N/A	84	96	93
Clinical (%)	100	N/A	100	N/A	100	99.8	100	100	100
Aspirin alone	No	Yes	No	Yes	No	No	Not reported	No	No
Aspirin + ticlopidine	98%	50%	No	Yes	No	No	Not reported	100%	No
Other	Anticoagulation 2%	Heparin + phenprocoumon	Aspirin + dextran + warfarin	Aspirin + coumadin	Aspirin + dextran + warfarin	Aspirin + dipyridamole + warfarin	Not reported	None	Aspirin + dipyridamole + warfarin

CCO, Centre for Cardiology Othmarschen, Hamburg, Germany; TUM, Technical University, Munich, Germany

TABLE 28 *Studies satisfying criteria for inclusion in the intra-observer reproducibility review*

Study	Number	Pre/post stenting	Diameter (mm) Mean difference ± SD	Area (mm^2) Mean difference ± SD	Frequency (MHz) Transducer type	Method of border definition
Kearney, *et al.*, 1997[114]	24 patients	Post stenting	Reference segments: proximal 0.03 ± 0.17; distal 0.00 ± 0.27	Reference segments –0.08 ± 0.8; minimal segment –0.01 ± 0.58	Not reported Mechanical	Manual
Mudra, *et al.*, 1994[115]	23 locations	Post stenting	All segments 0.02 ± 0.13	All segments 0.04 ± 0.33	20 64-element array	Manual

TABLE 29 *Studies in which the same image or only diseased segments were used to assess intra-observer reproducibility but which otherwise satisfied inclusion criteria*

Study	Number	Pre-/post-intervention	Same image measured?	Non-diseased reference segments?	Area (mm^2) Mean difference ± SD (Variability (%))	Frequency (MHz) Transducer type	Method of border definition
von Birgelen, *et al.,* 1996[116]	20	No intervention	Yes	No	0.87% ± 6.67%	Not reported Mechanical	Automated
von Birgelen, *et al.*, 1997[117]	30 segments	Pre- and post-PTCA/DCA	Yes	No	–0.4% ± 2.7%	30 Mechanical	Automated
von Birgelen, *et al.,* 1997[118]	10	Post-stenting	Yes	No	In stent, 0.0% ± 0.2%	30 Mechanical	Automated
Foster, *et al.*, 1997[119]	27 lesions	Pre-PTCA/DCA	Yes	No	0.48 ± 0.05	20 Not reported	Manual
Haussman, *et al.*, 1994[120]	119 images	Pre-PTCA	Yes	No	See text	30 Not reported	Manual
Nakatani, *et al.*, 1995[121]	10 sites	Pre- and post-glycerol trinitrate	Yes	Yes, only non-diseased	Systolic, 3.6% ± 3.2%	30 Mechanical	Manual
Nicosia, *et al.,* 1997[113]	23 segments	Post-stenting	Yes	No	0.1 ± 0.1	Automated Not reported	
Peters, *et al.*, 1996[122]	96 sites	Post-PTCA	Yes	No	Systolic, 0.06 ± 0.6	30 & 30 Rotating mirror & mechanical	Manual
Suzuki, *et al.*, 1996[123]	10 sites	Pre- and post-glycerol trinitrate	Yes	Yes	(1.6%)	30 Mechanical	Manual
Tsutsui, *et al.*, 1998[124]	10 segments	Post-PTCA	Yes	No	(4.7%)	30 Mechanical	Manual
Vavurankis, *et al.*, 1997[125]	10 sites	No intervention	Yes	Yes, only non-diseased	(3.5%)	20 Array	Manual
Weissman, *et al.,* 1995[126]	114 images	Pre- and post-DCA	Yes	Yes	Pre: 0.35 ± 1.22 Post: 0.04 ± 1.29	30 Not reported	Manual
Yamagishi, *et al.*, 1995[127]	10 sites	Pre- and post-glycerol trinitrate	Yes	Yes	(3.5%)	20 Array	Manual

TABLE 30 *Articles satisfying the criteria for inclusion in the interobserver reproducibility review*

Study	Number	Pre-/post-intervention	Non-diseased reference segments?	Area (mm^2) Mean difference ± SD	Frequency (MHz) Transducer (Variability (%))	Method of border definition type
von Birgelen, *et al.*, 1996[116]	20	No intervention	No	0.8% ± 7.28%	Not reported Mechanical	Automated
von Birgelen, *et al.*, 1997[117]	30 segments	Pre- and post-PTCA/DCA	No	0.4% ± 5.2%	30 Mechanical	Automated
von Birgelen, *et al.*, 1997[118]	10	Post-stenting	No	In stent: 0.0 ± 0.3	30 Mechanical	Automated
Foster, *et al.*, 1997[119]	27 lesions	Pre-PTCA/DCA	No	0.94 ± 0.08	20 Not reported	Manual
Haase, *et al.*, 1995[128]	40	Pre- and post-PTCA	No	Pre-: 0.48 ± 0.85 Post-: 0.79 ± 1.40 Both: 0.61 ± 1.0	Not reported	Automated
Haussman, *et al.*, 1994[120]	119 images	Pre-PTCA	No	See text	30 Mechanical	Manual
Kearney, *et al.*, 1997[114]	24 patients	Post-stenting	Yes	–0.18 ± 0.52	Not reported Mechanical	Manual
Nakatani, *et al.*, 1995[121]	10 sites	Pre- and post-glycerol trinitrate	Yes	Systolic: 5.6% ± 3.3%	30 Mechanical	Manual
Nicosia, *et al.*, 1997[113]	23 segments	Post-stenting	No	0.4 ± 0.4	Not reported	Automatic
Peters, *et al.*, 1996[122]	96 sites	Post-PTCA	No	Systolic: –0.1 ± 0.95	30 & 30 Rotating mirror & mechanical	Manual
Porter, *et al.*, 1993[129]	30 segments	Pre-PTCA	Yes	10% ± 9%	30 Mechanical	Manual
Suzuki, *et al.*, 1996[123]	10 sites	Pre- and post-glycerol trinitrate	Not reported	(0.6%)	30 Mechanical	Manual
Tsutsui, *et al.*, 1998[124]	10 segments	Post-PTCA	No	(6.6%)	30 Mechanical	Manual
Vavurankis, *et al.*, 1997[125]	10 sites	No intervention	Yes	(3.9%)	20 Array	Manual
Yamagishi, *et al.*, 1995[127]	10 sites	Pre- and post-glycerol trinitrate	Yes	(4.2%)	20 Array	Manual

Absolute numbers of units of each consumable used are shown in *Table 37*, and stent-usage data reported in the literature are summarised in *Table 38*.

The incremental costs per patient (consumables and staff) for IVUS guidance, based on the 1998 figures from the Leeds Teaching Hospitals NHS trust, for unit costs of consumables and a capacity of 800 patients are shown in *Tables 39* and *40*. Estimates of staff resource utilisation were calculated from the procedural time, using hourly rates and assuming that four staff were present in all cases: nurse, technician, radiographer and cardiologist or radiologist.

TABLE 31 *Restenosis branch: 6-month angiographic outcome findings for three studies of IVUS-guided stenting included in the decision model*

Study	Total number of patients	Restenosis	Symptomatic	Asymptomatic	Repeat PTCA	CABG
de Jaegere, *et al.*, 1998[44]	157	12	7	5	7	0
Jeremias, *et al.*, 1999[137]	43	15	5	10	Not reported	Not reported
Serruys, *et al.*, 1998[143]	165	19	11	8	11	1
Total	365	46	23	23	18	1

TABLE 32 *MACE branch: 6-month clinical outcome findings for three studies of IVUS-guided stenting included in the decision model*

Study	Total number of patients	MACE	Dead	MI	TLR	Repeat PTCA	CABG
de Jaegere, *et al.,* 1998[44]	157	10	0	6	6	4	2
Jeremias, *et al.*, 1999[137]	43	0	0	0	0	0	0
Serruys, *et al.*, 1998[143]	165	4	1	4	2	2	0
Total	365	14	1	10	8	6	2

TABLE 33 *Restenosis branch: 6-month angiographic outcome findings for two studies of non-IVUS-guided stenting included in the decision model*

Study	Total number of patients	Restenosis	Symptomatic	Asymptomatic	Repeat PTCA	CABG
Fischman, *et al.,* 1994[34]	205	56	21	35	*	*
Serruys, *et al.*, 1994[33]	249	52	30	22	*	*
Total	454	108	51	57	50[a]	3[a]

**Not possible to extract from data presented*

[a] Estimated by assuming that the proportion of patients undergoing each alternative is the same as that for the corresponding part of the IVUS-guidance branch

TABLE 34 *MACE branch: 6-month clinical outcome findings from two non-IVUS-guided stenting studies included in the decision model*

Study	Total number of patients	MACE	Dead	MI	TLR	Repeat PTCA	CABG
Fischman, *et al.*, 1994[34]	205	*	*	*	*	*	*
Serruys, *et al.*, 1994[33]	249	*	*	*	*	*	*
Total	454	33[a]	5[a]	24[a]	23[a]	8[a]	15[a]

**Not possible to extract from data presented*

[a] Only total event rates, combining both angiographic and clinical follow-up, were reported. Clinical outcome rates were estimated by assuming that the proportion of patients experiencing each alternative was the same as that for the corresponding part of the IVUS-guidance branch

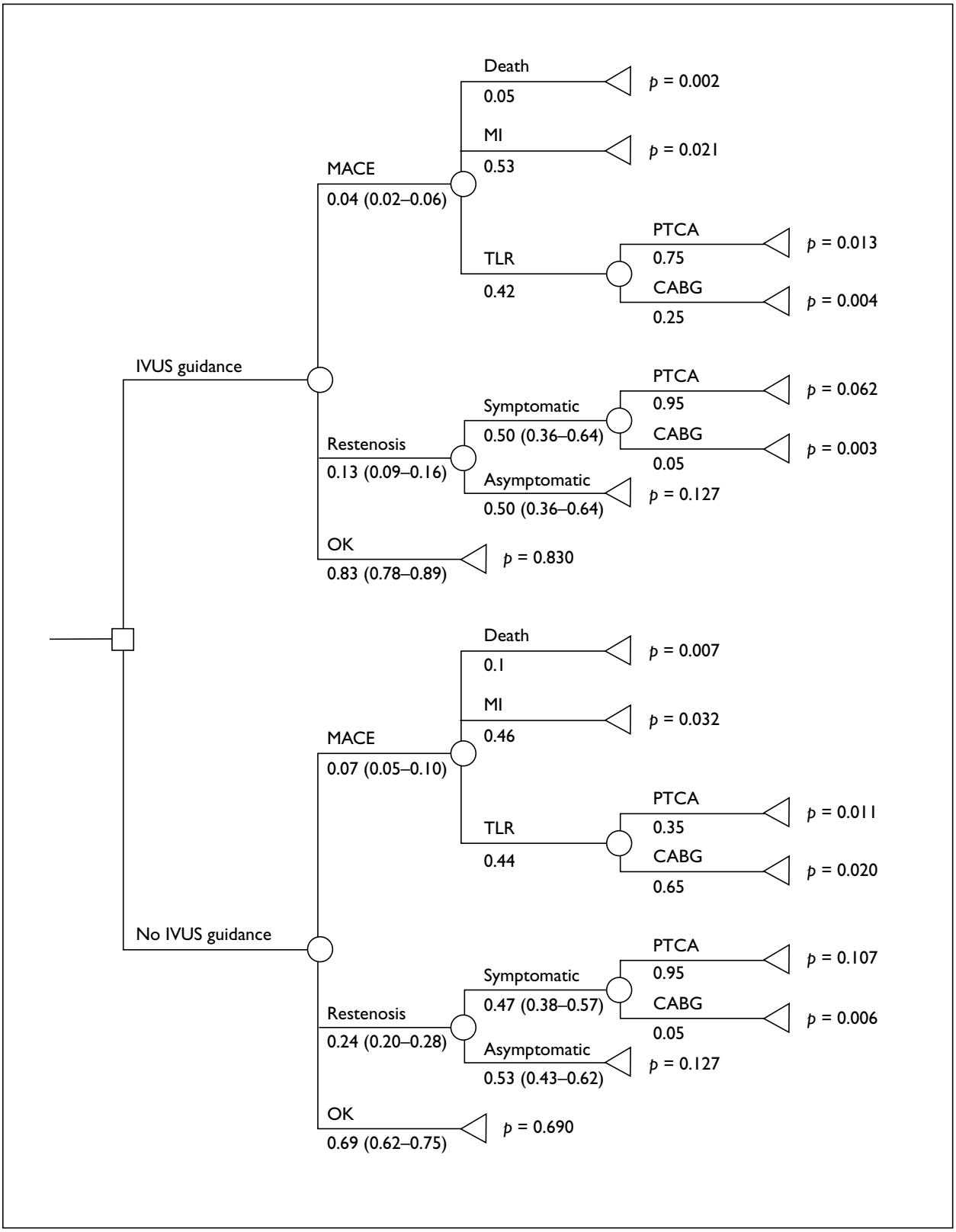

FIGURE 3 *Probabilities assigned to each branch of the decision tree. Each branch point on the tree is a decision point representing either a clinical decision (□) or a chance event (○). Final outcome points are represented by a triangle (◁)*

TABLE 35 *Procedural details for 19 patients undergoing IVUS-guided stenting*

Year of birth	Gender	Pre-procedure diagnosis	Procedure	Time (minutes)
1926	Male	Unstable angina	Urgent	110
1921	Female	Stable angina	Elective	150
1941	Male	Stable angina	Elective	85
1938	Male	Stable angina	Elective	175
1935	Male	Stable angina	Elective	135
1934	Male	Stable angina	Elective	125
1927	Female	Unstable angina	Elective	65
1932	Male	Stable angina	Elective	90
1945	Male	Stable angina	Elective	80
1938	Female	Stable angina	Elective	165
1941	Male	Stable angina	Elective	150
1934	Female	Stable angina	Elective	105
1962	Male	Stable angina	Elective	80
1930	Male	Stable angina	Elective	90
1939	Female	Stable angina	Elective	140
1949	Male	Unstable angina	Urgent	170
1939	Male	Stable angina	Elective	135
1930	Female	Stable angina	Elective	120
1943	Male	Stable angina	Elective	115
			Mean time in laboratory ± SD	120.3 ± 7.6

TABLE 36 *Procedural details for 19 matched patients undergoing stenting without IVUS guidance*

Year of birth	Gender	Pre-procedure diagnosis	Procedure	Time (minutes)
1927	Male	Stable angina	Elective	90
1928	Male	Stable angina	Elective	185
1937	Female	Stable angina	Elective	80
1943	Male	Stable angina	Elective	85
1939	Male	Stable angina	Elective	95
1915	Female	Stable angina	Elective	150
1939	Male	Stable angina	Elective	105
1940	Female	Unstable angina	Elective	75
1943	Male	Stable angina	Elective	95
1951	Male	Stable angina	Elective	65
1927	Female	Stable angina	Elective	60
1936	Female	Stable angina	Elective	120
1933	Male	Stable angina	Elective	75
1940	Male	Unstable angina	Urgent	45
1938	Female	Stable angina	Elective	60
1950	Male	Stable angina	Elective	70
1932	Female	Stable angina	Elective	90
1944	Male	Stable angina	Elective	100
1949	Male	Unstable angina	Urgent	185
			Mean time in laboratory ± SD	96.3 ± 9.0

TABLE 37 *Consumables used for the two groups of 19 patients from the Leeds Teaching Hospitals NHS Trust*

Consumable	IVUS-guided	Not IVUS-guided	Excess number used for IVUS guidance
Stents	29	31	–2
Balloons	48	27	21
Guides	43	30	13
Sheaths	44	42	2
Iohexol	5	0	5
Iopromide	25	27	–2
Sodium amidotrizoate (Urographin®, Schering)	19	18	1
Iodixanol	2	1	1
Wire	41	45	–4

TABLE 38 *Stent usage per patient*

Study	Number of stents per patient		
	IVUS-guided	Not IVUS-guided	Excess number used for IVUS guidance
Albiero, *et al.*, 1997[138]	1.28	1.18	0.10
Blasini, *et al.*, 1998[139]	1.73	1.40	0.33
Fitzgerald, *et al.*, 1999[105]	1.50	1.55	–0.05
Leeds Teaching Hospitals NHS Trust study[79]	1.53	1.63	–0.1
Mean	1.51	1.44	0.07

TABLE 39 *Consumables: incremental cost of IVUS guidance per patient*

Consumable	Unit cost (£)	IVUS guidance (units per patient)	No IVUS guidance (units per patient)	Incremental cost of IVUS guidance per patient (£)
Stents	553.00	1.51	1.44	38.71
Balloons	257.00	2.53	1.42	285.27
Guides	70.38	2.26	1.58	47.86
Sheaths	19.86	2.32	2.21	2.18
Wires	78.00	2.16	2.37	16.38
Iohexol	11.93	0.26	0	3.10
Iopromide	71.67	1.32	1.42	7.17
Sodium amidotrizoate (Urographin)	17.00	1	0.95	0.85
Iodixanol	9.74	0.11	0.05	0.58
Total	–	–	–	355.00

TABLE 40 *Staff: incremental cost of IVUS guidance per patient*

Staff	Unit cost (£/hour)	IVUS guidance (units/patient)	No IVUS guidance (units/patient)	Incremental cost of IVUS guidance per patient (£)
Nurse	10	2.01	1.61	4.00
Technician	12	2.01	1.61	4.80
Radiographer	13	2.01	1.61	5.20
Consultant cardiologist/radiologist	33	2.01	1.61	13.20
Total	68	2.01	1.61	27.20

TABLE 41 *Fixed costs: incremental cost of IVUS guidance per patient*

Fixed cost item	Cost (£)	Annual cost (£)	Incremental cost of IVUS guidance per patient (£)
Capital – 40% staff (see *Table 40*)	–	–	10.88
IVUS equipment	65,000	15,430	19.29
Total	–	–	30.17

Fixed costs for capital and equipment are presented in *Table 41*.

The total incremental intervention cost per patient for IVUS guidance, given by the sum of consumables, staff and capital costs, was £412.

Conclusion

Results of applying the search strategies have been presented to demonstrate the returns from the various resources used. Details of studies included in the review are given, together with short descriptive summaries of those involving IVUS-guided stenting. Data drawn from the literature and the empirical study for use in the decision-analytic model are presented. In the next chapter, the reasons for the exclusion of studies from the review are presented. Results that were drawn from the literature or calculated using the model, and address the research questions from chapter 2, are presented in chapter 6.

Chapter 5

Studies excluded from the review

IVUS-guided interventions

The reasons for the exclusion of 64 articles[47,88,92–98,101,118,145,150–200] that satisfied the electronic, manual and final criteria, but did not satisfy one or more of the criteria set out in *Table 2,* are given in *Table 42.*

Control arm

The reasons for exclusion of 22 articles[201–222] that did not satisfy the relevance and validity criteria described in chapter 3 are given in *Table 43.*

Additional topics

In-stent restenosis

All the studies considered for inclusion were excluded because they did not address the role of IVUS in guiding treatment choice.[91,93,114–115,132,134–136,142,152,154,168,169,171,173,174,184,196,199,223–244]

Reproducibility

The reasons for exclusion of 25 articles[40,169,177,245–266] that did not satisfy the inclusion criteria described in chapter 3 are given in *Table 44.*

Economics

No article was found in which health economics in the subject area was investigated.

TABLE 42 *Excluded articles on IVUS-guided intervention (64 articles)*

Study	Exclusion criteria*							
	Patient group		Clinical follow-up			Angiographic follow-up		
	Not ITT	Overlap	None	< 85%	Too little information	None	< 85%	Not 6 months
Akiyama, *et al.*, 1998[150]	Yes							
Albiero, *et al.*, 1997[151]	Yes	Yes						
Berger, *et al.*, 1998[152]	Yes							
Blasini, *et al.*, 1996[153]		Yes						
Blasini, *et al.*, 1997[154]			Yes			Yes		
Colombo, *et al.*, 1995[144]		Yes						
Colombo, *et al.*, 1996[155]		Yes						
Colombo, *et al.*, 1997[156]		Yes						
De Benedictis, *et al.*, 1998[157]				Yes			Yes	
De Jaegere, *et al.*, 1996[158]		Yes						
De Lezo, *et al.*, 1993[159]			Yes				Yes	
Di Mario, *et al.*, 1997[160]	Yes							
Di Mario, *et al.*, 1998[161]	Yes							
Gil, *et al.*, 1996[162]			Yes			Yes		
Goldberg, *et al.*, 1994[163]			Yes			Yes		
Goldberg, *et al.*, 1995[164]	Yes							
Gorge, *et al.*, 1995[165]			Yes			Yes		
Hall, *et al.*, 1994[166]		Yes						
Hall, *et al.*, 1995[167]		Yes						
Heublein, *et al.*, 1998[168]	Yes							
Hoffmann, *et al.*, 1996[169]	Yes							
Hoffmann, *et al.*, 1998[170]			Yes			Yes		
Hong, *et al.*, 1998[171]					Yes	Yes		
Honye, *et al.*, 1994[172]			Yes			Yes		
Itoh, *et al.*, 1997[173]	Yes							
Itoh, *et al.*, 1997[192]	Yes	Yes						
Kasaoka, *et al.*, 1998[174]		Yes						
Kastrati, *et al.*, 1997[175]	Yes							
Kawata, *et al.*, 1997[176]			Yes			Yes		
Kawata, *et al.*, 1998[93]			Yes			Yes		
Kudo, *et al.*, 1997[101]			Yes					Yes
Lee, *et al.*, 1995[177]			Yes			Yes		
Mahrholdt, *et al.*, 1998[94]		Yes						
Mathew, *et al.*, 1997[178]	Yes							
Mintz, *et al.*, 1994[179]			Yes			Yes		
Mintz, *et al.*, 1996[180]			Yes			Yes		
Mintz, *et al.*, 1996[47]			Yes					Yes
Moussa, *et al.*, 1997[181]	Yes							
Moussa, *et al.*, 1997[182]	Yes							
Moussa, *et al.*, 1998[183]	Yes							
Moussa, *et al.*, 1998[184]		Yes						
Mudra, *et al.*, 1997[185]				Yes			Yes	
Muller, *et al.*, 1997[186]			Yes			Yes		

* *See Table 2*

continued

TABLE 42 contd *Excluded articles on IVUS-guided intervention (64 articles)*

Study	Exclusion criteria*							
	Patient group		Clinical follow-up			Angiographic follow-up		
	Not ITT	Overlap	None	< 85%	Too little information	None	< 85%	Not 6 months
Nakamura, *et al.*, 1994[187]			Yes			Yes		
Neuerburg, *et al.*, 1991[95]			Yes			Yes		
Pan, *et al.*, 1996[188]	Yes							
Pan, *et al.*, 1997[189]	Yes							
Prati, *et al.*, 1996[190]			Yes			Yes		
Prati, *et al.,* 1997[191]			Yes			Yes		
Reimers, *et al.*, 1998[192]	Yes							
Saito, *et al.*, 1995[96]					Yes			Yes
Simonton, *et al.*, 1998[193]	Yes							
Stone, *et al.*, 1997[194]			Yes			Yes		
Sumitsuji, *et al.*, 1995[97]			Yes			Yes		
Talley, *et al.*, 1996[195]			Yes			Yes		
Thuesen, *et al.*, 1997[88]					Yes			Yes
Tsukahara, *et al.*, 1996[98]			Yes			Yes		
van Sambeek, *et al.*, 1998[196]			Yes			Yes		
Violaris, *et al.*, 1992[197]			Yes			Yes		
von Birgelen, *et al.,* 1997[118]			Yes			Yes		
Werner, *et al.*, 1997[198]					Yes	Yes		
Werner, *et al.,* 1997[199]			Yes			Yes		
Wolfhard, *et al.*, 1998[200]			Yes			Yes		
Totals	19	13	28	2	4	27	3	4
	30		34			34		

*See *Table 2*

TABLE 43 *Control arm: excluded articles (22 articles)*

Study	Acronym
Not native coronary arteries (1)	
Savage, *et al.,* 1997[201]	SAVED
Not elective stenting procedure (6)	
De Muinck, *et al*., 1994[202]	
Lincoff, *et al*., 1993[203]	
Stauffer, *et al*., 1995[204]	
Stauffer, *et al*., 1995[205]	
Danchin, *et al*., 1995[206]	
Scott, *et al*., 1993[207]	
Chronic occlusion (3)	
Rubartelli, *et al.,* 1998[208]	GISSOC
Sirnes, 1996[209]	SICCO
Hancock, *et al*., 1998[210]	
Acute MI (4)	
Rodriguez, *et al*., 1998[211]	GRAMI
Antoniucci, *et al*., 1998[212]	FRESCO
Suryapranata, *et al*., 1998[213]	
Bar, *et al*., 1993[214]	START
No follow-up (4)	
Foley, *et al*., 1995[215]	
Foley, *et al*., 1995[216]	
De Jaegere, *et al*., 1993[217]	
Kimura, *et al*., 1993[218]	
IVUS guidance used on some patients (1)	
Serruys, *et al*., 1998[221]	Benestent II
One named coronary artery (2)	
Versaci, *et al*., 1997[219]	
Eeckhout, 1996[220]	
Primary article could not be found (1)	
Goy & Eeckhout[222] mention but no primary publication identified	REST

TABLE 44 *Reproducibility: excluded articles (25)*

Study
Not native coronary vessels (3)
Berglund, *et al*., 1996[245]
Mintz, *et al*., 1995[246]
Nishioka, *et al*., 1996[247]
Reproducibility refers only to angiography (3)
Bermejo, *et al*., 1998[248]
Nishimura, *et al*., 1995[249]
Hermiller, *et al*., 1993[40]
Measurements reported do not include diameter or area (10)
Bouma, *et al.,* 1997[250]
Fuessl, *et al*., 1996[251]
Hoffmann, *et al*., 1996[169]
Kimura, *et al*., 1996[252]
Koyama, *et al*., 1995[253]
Masseroli, *et al*., 1998[254]
Mizushige, *et al*., 1997[255]
von Birgelen, *et al*., 1997[256]
Yamagishi, *et al*., 1994[257]
Yamagishi, *et al*., 1996[258]
Not using paired differences (9)
Ge, *et al*., 1994[259]
Ge, *et al*., 1994[260]
Jain, *et al*., 1994[261]
Lee, *et al*., 1995[177]
Nakamura, *et al*., 1995[262]
Nakamura, *et al*., 1996[253]
Tanaglia, *et al*., 1992[264]
Weissman, *et al*., 1995[265]
Zamorano, *et al*., 1994[266]

Chapter 6

Results of the review

The results of the review are arranged under each topic by research question (see chapter 2).

IVUS-guided primary stenting

Does IVUS guidance improve outcomes compared with the procedure without IVUS guidance?

Results from the literature

6-month outcome The results from the seven articles[44,115,137-139,142,143] in which the performance of IVUS-guided stenting was addressed, and which contained information on clinical or angiographic follow-up at 6 months, are summarised in *Table 45*.

The angiographic restenosis rate at 6 months, derived from the seven articles was 16 ± 1% (108/682). The MACE rate at 6 months, including events following symptomatic angiographic restenosis, was given in three articles,[44,137,142] and the overall figure was 11 ± 2% (41/365).

Note that these values have been derived from a mixture of study types. Three articles described observational studies;[44,115,142] three articles[138,139,142] described controlled trials (one RCT, two matched) of IVUS-guided stenting versus non IVUS-guided stenting. The remaining article[137] described an RCT of final look IVUS-guided versus stepwise IVUS-guided stenting. Information was drawn only from the final look arm and should be regarded as observational. Indeed, as was noted in chapter 4, most of the included studies were flawed in some way; the validity of their conclusions is discussed further in chapter 8.

TABLE 45 *Outcome findings at 6 months in seven IVUS-guided stenting studies*

Study	Number of patients	Angiographic follow-up				Clinical follow-up				
		Total restenosis	Symptomatic restenosis	Repeat PTCA	CABG	MACE	Death	MI	Repeat PTCA	CABG
Albiero, *et al.*, 1997[138]	97	22	Not reported	Not reported	Not reported	*	*	*	*	*
Blasini, *et al.*, 1998[139]	125	22	Not reported	Not reported	Not reported	Not reported	1	Not reported	Not reported	Not reported
De Jaegere, *et al.*, 1998[44]	157	12	7	7	0	10	0	6	2	2
Jeremias, *et al.*, 1999[137a]	43	15	5	Not reported	Not reported	0	0	0	0	0
Mudra, *et al.*, 1994[115]	16	2	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Schiele, *et al.*, 1998[142]	79	16	Not reported	Not reported	Not reported	Not reported	1	Not reported	Not reported	Not reported
Serruys, *et al.*, 1994[33]	165	19	12	11	1	7	1	4	2	0
Total	724	122	–	–	–	–	–	–	–	–

* *Not possible to extract from data presented*

[a] *'Final look' IVUS*

TABLE 46 *Outcome findings at 6 months in five non IVUS-guided stenting studies*

Study	Number of patients	Angiographic follow-up				Clinical follow-up					Total				
		Restenosis	Symptomatic restenosis	Repeat PTCA	CABG	MACE	Death	MI	Repeat PTCA	CABG	MACE	Death	MI	Repeat PTCA	CABG
Albiero, *et al.*, 1997[138]	97	23	Not reported	Not reported	Not reported	*	*	*	*	*	*	*	*	*	*
Blasini, *et al.*, 1998[139]	125	32	Not reported	Not reported	Not reported	Not reported	2	Not reported	Not reported	Not reported	Not reported	2	Not reported	Not reported	Not reported
Fischman, *et al.*, 1994[34]	205	56	Not reported	Not reported	Not reported	*	*	*	*	*	40	3	13	23	10
Schiele, *et al.*, 1998[142]	76	21	Not reported	Not reported	Not reported	Not reported	1	Not reported	Not reported	Not reported	Not reported	1	Not reported	Not reported	Not reported
Serruys, *et al.*, 1994[33]	249	52	Not reported	Not reported	Not reported	*	*	*	*	*	44	5	24	58	18
Total	752	184	–	–	–	–	–	–	–	–	–	–	–	–	–

*Not possible to extract from data presented

TABLE 47 *Outcome findings at more than 6 months in two IVUS-guided stenting studies*

Study	Number of patients	Angiographic follow-up				Clinical follow-up					
		Total restenosis	Symptomatic restenosis	Repeat PTCA	CABG	MACE	Death	MI	Repeat PTCA	CABG	TLR
Follow-up at 9 months											
Fitzgerald, *et al.*, 1999[105]	270	Not reported	Not reported	Not reported	Not reported	42	0	19	Not reported	Not reported	23
Follow-up at 1 year											
Carrozza, *et al.*, 1998[140]	49	Not reported	Not reported	Not reported	Not reported	5	0	4	3	0	1

For comparison, the 6-month outcome results from five included articles on non-IVUS-guided stenting[33,34,138,139,142] are summarised in *Table 46*. The angiographic restenosis rate at 6 months derived from the five studies was 24 ± 2% (184/752). The MACE rate at 6 months was given in two articles;[33,34] the mean value was 19 ± 2% (84/454).

In this case, two studies[33,34] were RCTs in which PTCA alone was compared with PTCA and stenting, and one[142] was an RCT in which the use of stents was compared with high-pressure deployment alone. The other two[138,139] were RCTs on IVUS-guided stenting; however, because of the way in which data are used here, they should be regarded as observational studies.

The rate of angiographic restenosis at 6 months was 8% less (95% CI, 4 to 12) with the use of IVUS guidance.

Long-term outcome Information on clinical or angiographic follow-up was presented in two articles[105,140] on IVUS-guided stenting for periods over 6 months. Results are summarised in *Table 47*. Neither article reported restenosis rates. The MACE rate was given in both but, as their follow-up periods differed, no calculation of a mean value was made.

Information on clinical follow-up was presented in four articles[107,145–147] on non IVUS-guided stenting for periods over 6 months. Results are summarised in *Table 48*. None of the articles reported on angiographic restenosis rates.

Results from modelling

6-month outcome The probabilities and costs used in modelling are shown on the decision tree in *Figure 4*. They are slightly different from the values presented in the previous section, as data were drawn from a limited subset of the articles for use in the model.

The restenosis rate in the control arm is 0.24, while in the IVUS-guidance arm it is 0.13. The absolute reduction in restenosis rate from IVUS guidance is therefore 0.11. The MACE rate is 0.07 in the control arm and 0.04 in the IVUS-guidance arm. The absolute reduction in adverse events from IVUS guidance is therefore 0.03.

Extrapolation to long-term outcome The long-term incremental QALY gain is given by:

$$QALY_{IVUS} = QpR \times (\text{absolute reduction in restenosis rate})_{IVUS} \quad (7)$$

where QpR = 0.24 (the literature[85] value as described in chapter 3) and absolute reduction in restenosis rate from IVUS guidance = 0.11. So the long-term incremental QALY gain was 0.0264 years.

Is the technology cost-effective in the application?

Results from the literature

No articles were included in the review as none were found that satisfied the inclusion criteria.

Results from modelling

From the decision model, the outcome cost per patient of an IVUS-guided stenting intervention was found to be £281. The corresponding figure for no IVUS guidance was £523, so the incremental outcome cost of IVUS guidance was –£242. The total incremental cost per patient of an IVUS-guided stenting intervention (the sum of the incremental outcome cost and the incremental intervention cost) was therefore £170 (–£242 + £412).

TABLE 48 *Outcome findings at more than 6 months in four non IVUS-guided stenting studies*

Study	Number of patients	Any event	Total event rate				
			Death	MI	Repeat PTCA	CABG	TLR
Follow-up at 9 months							
Fitzgerald, *et al.*, 1999[105]	229	Not reported	2	14	*	*	35
Follow-up at 1 year							
George, *et al.*, 1998[147]	205	51	3	13	39	12	43
Macaya, *et al.*, 1996[148]	259	60	3	14	45	21	Not reported
Savage, *et al.*, 1998[149]	163	36	1	10	27	11	26

* *Not possible to extract from data presented*

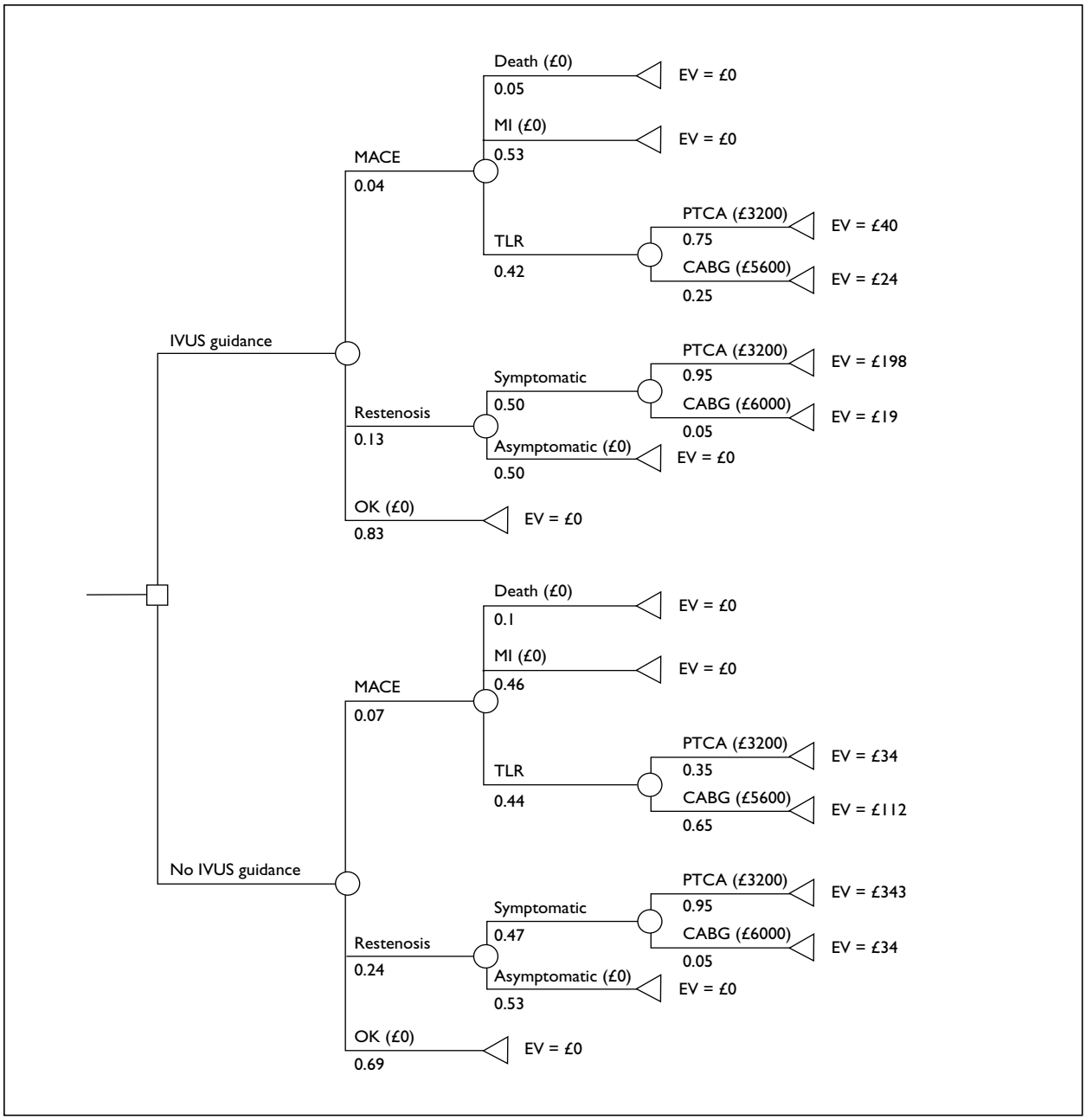

FIGURE 4 *Complete decision tree, including costs and the expected value (EV) of final outcomes found by running the model. The outcome cost associated with the IVUS-guidance arm is £281 and the outcome cost associated with the no-IVUS-guidance arm is £523 (□, clinical decision; ○, chance event; ◁, final outcome point)*

This may be expressed as an ICER using equation 3:

$$\text{ICER}_{re} = (\text{total incremental cost per patient})/(\text{absolute reduction in restenosis rate}) \quad (3)$$
$$= £170/0.11$$
$$= £1545 \text{ per restenosis event avoided.}$$

Extrapolation to long-term outcome The estimated incremental QALY gain was 0.0264 years and the cost per restenosis event avoided (ICER_{re}) was £1545. From equation 8, the long-term cost per QALY (ICER_{QALY}) was £170/(0.24 × 0.11) = £6439. If cost-effectiveness is assumed for costs below £10,000 per QALY, then IVUS-guided stenting has been shown to be cost-effective. IVUS-guided stenting will be cost-effective for a limit of £10,000 per QALY if the absolute reduction in restenosis rate is above 0.07 or the total incremental cost per patient is under £264 (from equation 8, assuming a fixed value of 0.24 for QALY per restenosis event avoided, with baseline values of £170 for the total incremental cost per patient and 0.11 for the absolute reduction in restenosis rate). The relationship between the reduction in restenosis rate and the total incremental cost per patient allowable to maintain cost-effectiveness is shown in *Figure 5*.

Is there any morbidity associated with the use of IVUS?

Results from the literature

There was very little evidence about the morbidity of IVUS-guided procedures. The only article to report the occurrence of IVUS-related complications was the MUSIC[44] study, in which one case of dissection occurred in 155 patients receiving IVUS guidance (0.6%).

What is the failure rate of IVUS examination in the application?

Results from the literature

It was not possible to answer this question from the literature. In six articles included in the review,[105,115,137–139,141] 100% of patients had an IVUS examination as it was an inclusion criterion for the study that patients should have undergone a successful IVUS examination. In the remaining articles,[44,140,142,143] failure rates were not broken down and 27 from 450 patients enrolled (6%) did not have IVUS guidance. The reason for a

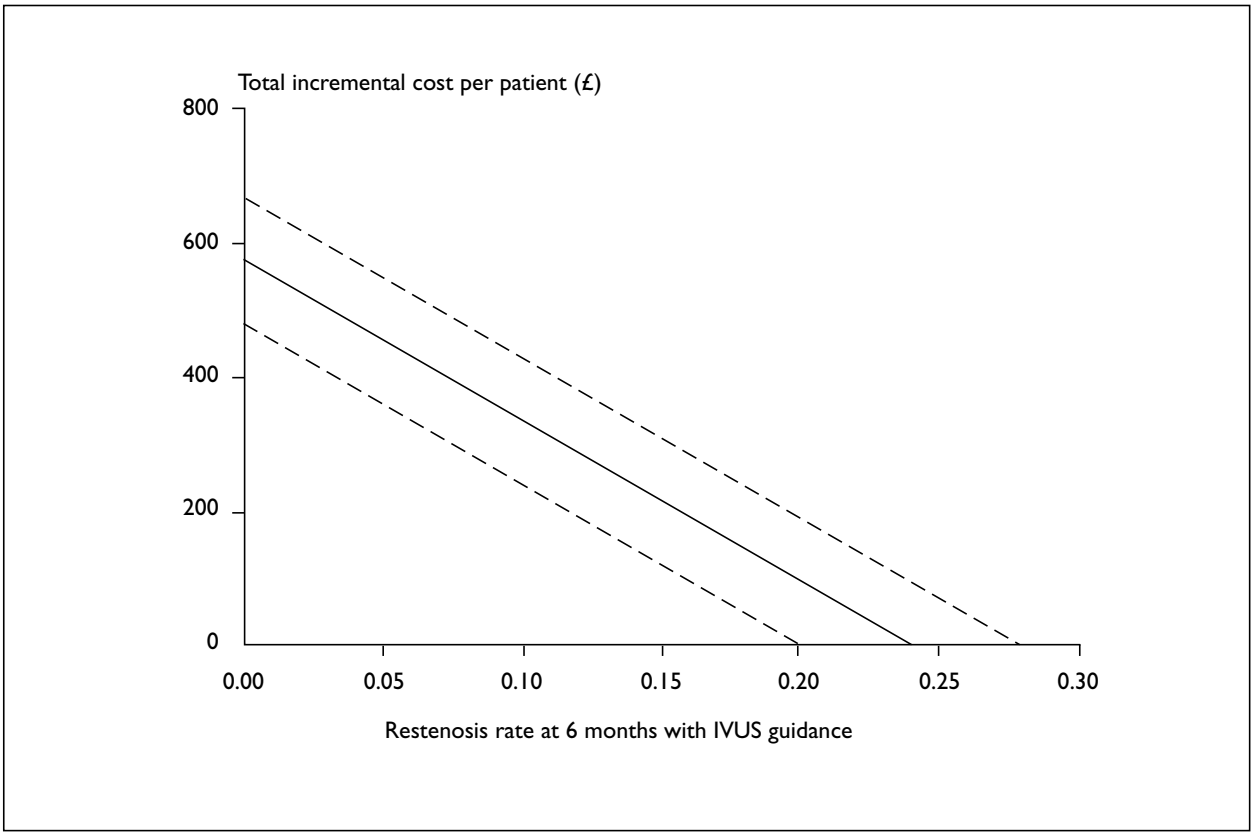

FIGURE 5 *Total incremental cost per patient to maintain cost-effectiveness (£10,000 per QALY) for a range of restenosis rates achieved with IVUS guidance. The lines show the maximum cost that is cost-effective for three fixed values of the restenosis rate without IVUS guidance, while the area under the lines is the region of cost effectiveness. The dashed lines were calculated with the restenosis rate without IVUS guidance maintained at the 95% CIs (0.20 to 0.28) while the solid line is calculated using the baseline rate of 0.24*

patient not having an IVUS examination might have been equipment unavailability rather than a failed procedure.

IVUS-guided optimisation of PTCA

Only one study[130] was included in the review that addressed IVUS-guided optimisation of PTCA. The article reported an angiographic restenosis rate at 6 months of 21% but, as only 75% of patients were followed-up, the result is inconclusive. There was insufficient evidence in the literature to answer the questions on outcomes, cost-effectiveness, morbidity and failure rate associated with IVUS-optimised PTCA. No modelling was performed for IVUS-guided optimisation of PTCA because of the lack of published information.

Other IVUS-guided coronary interventions

No articles were included in the review addressing other IVUS-guided coronary interventions. There was insufficient evidence in the literature to answer the questions on the associated outcomes, cost-effectiveness, morbidity and failure rate. No modelling was performed for other IVUS-guided coronary interventions because of the lack of published information.

IVUS-guided therapy for in-stent restenosis

No articles were included in the review addressing IVUS-guided therapy for in-stent restenosis. There was insufficient evidence in the literature to answer the questions on the associated outcomes, cost-effectiveness, morbidity, failure rate or therapeutic impact. No modelling was performed because of the lack of published information.

What are the *in-vivo* intra- and inter-observer reproducibilities of measurements made using IVUS?

Using only those articles that satisfied all the inclusion criteria, the worst case intra-observer reproducibility[114] was for reference segments, where the difference in area was found to be -0.08 ± 0.8 mm^2. For measurements within the stent, the corresponding result was -0.01 ± 0.58. From the former result, it can be concluded that the minimum change in area that can be measured by a single observer is 1.6 mm^2.

Rather more articles were included in the inter-observer reproducibility category. They fell into two groups, those using manual tracing of the border and those using automated techniques to define the border. In the manual tracing group, the results of three studies[114,119,122] were reported as a mean area difference. The worst-case SD of differences post stenting was $\pm$ 0.95 mm^2, so our conclusion is that the minimum change in area that can be measured by different observers is 1.9 mm^2. In the automated tracing group, the results of three articles[113,118,128] were reported as a mean area difference. The worst-case SD of differences post stenting was $\pm$ 1.40 mm^2, so our conclusion is that the minimum change in area that can be measured automatically by different observers is 2.7 mm^2.

Chapter 7

Sensitivity analysis

Sensitivity analysis was used to investigate the effect on the final results of changes in the value assigned to selected parameters. Analysis was performed both for the calculation of the incremental intervention cost of IVUS-guided stenting and for the incremental outcome cost and event rates found using modelling.

Methods

One-way and scenario analyses were performed to determine the effect of changes in the value of selected parameters of the intervention cost calculation and in the decision-analytic model. The best-case situation[267] for IVUS guidance was defined as the one in which the value for the parameter in the IVUS-guidance arm was the best in the CI (for example, lowest restenosis rate) and the value for the parameter in the no-IVUS-guidance arm was the worst in the CI. Similarly, the worst-case situation was the one where the value for the IVUS-guidance arm was the worst, while that for the no-IVUS-guidance arm was the best. This approach to defining the best- and worst-case situations, in which new values were selected for both arms, was chosen in preference to one in which the value in one arm is fixed because there was uncertainty in both arms of the model. Parameter values for both IVUS guidance and the control arm were assigned to represent best- and worst-case situations, while the baseline estimate was the value previously used in the analysis.

One-way analysis

The calculation or model was run repeatedly, each time changing the value of only one parameter and keeping the others at their baseline value. Three runs were performed for each parameter for the best-case, baseline and worst-case values.

Scenario analysis

The calculation or model was run three times. For the first run all parameters were set to their best-case values, in the second all parameters were set to their baseline values, and for the third all parameters were set to their worst-case values.

In any branch in which the value of a parameter was changed, the probabilities of the alternative events were adjusted to ensure that the sum remained 1.0.

Costs of IVUS-guided intervention

The parameters included in the analysis were the number of stents per patient, number of balloons per patient and the time taken. All values, except those for the number of stents used, were taken from the empirical study. The calculation was made to assess the impact on the intervention cost per patient. The incremental cost of IVUS guidance was defined so that a positive cost represented a higher cost for IVUS-guided interventions than for non-IVUS-guided interventions.

6-month outcome

The parameters included in the analysis were restenosis rate, symptomatic restenosis rate and MACE rate. The model was run to assess the impact on the adverse events avoided, outcome costs per patient, restenosis events avoided, total IVUS incremental cost and $ICER_{re}$.

The way in which results were reported in the included articles meant that it was not possible to perform the best-/worst-case analysis for the parameters TLR rate and repeat PTCA rate, which occur in the MACE branch. Instead a limited analysis was performed. Results for the TLR rate at 9 months were taken from a single study[105] that was designed to measure the difference in TLR rate with and without IVUS guidance. Analysis was performed using these results and with the values for the other parameters set to their baseline values.

The repeat PTCA rate was investigated only by setting the rate for the no-IVUS-guidance arm to the same value as that used in the IVUS-guidance arm. This value was in agreement with results reported by Cohen and colleagues.[85] Analysis was performed with all other parameters set to their baseline values.

Extrapolation to long-term outcome

The method used to extrapolate to long-term outcome used data taken from only one article.[85]

As it was not possible to determine best and worst cases for one-way or scenario analysis, a threshold analysis was performed instead. The results were presented in chapter 6.

Results

Costs of IVUS-guided intervention

The ranges of parameter values used in the analyses are shown in *Table 49*.

The baseline incremental intervention cost was £412. One-way analyses gave ranges from a saving of £2 to a cost of £827 resulting from variations in stent and balloon usage, staff and capital costs (*Table 50*).

The scenario analysis (*Table 51*) showed that the incremental intervention cost could range from a saving of £341, through a baseline cost of £412, to a cost of £879.

6-month outcome

The absolute change in restenosis rate could range from a reduction of 0.19 through a baseline reduction of 0.11 to a reduction of 0.04 (*Table 52*). The MACE rate could range from a reduction of 0.08 through a baseline reduction of 0.03 to an increase of 0.01 (*Table 52*). From the one-way analysis (*Table 53*) on restenosis rate, the incremental outcome cost per patient ranges from a saving of £372 through a baseline saving of £242 to a saving of £130. In the scenario analysis (*Table 54*), the incremental outcome cost per

TABLE 49 *Ranges of parameter values used for sensitivity analysis of the intervention cost calculation*

	Number of stents per patient			Number of balloons per patient			Time (hours)		
	Best	Baseline	Worst	Best	Baseline	Worst	Best	Baseline	Worst
IVUS guidance	1.15	1.51	1.87	1.42	2.53	2.53	1.75	2.01	2.26
No IVUS guidance	1.83	1.44	1.05	1.42	1.42	1.42	1.91	1.61	1.31

NB: The values for numbers of balloons are not 95% CIs as data were only available from the empirical study, for which the best and worst case scenarios were defined using the value from the other arm of the study

TABLE 50 *Results of one-way analysis for the intervention cost calculation*

	Parameter costs (£)			Total intervention costs from one-way analysis (£)		
	Best	Baseline	Worst	Best	Baseline	Worst
Stents						
IVUS guidance	635	835	1034	1986	2185	2385
No IVUS guidance	1012	796	581	1988	1773	1557
Increment	–376	39	453	–2	412	827
Balloons						
IVUS guidance	365	650	650	1900	2185	2185
No IVUS guidance	365	365	365	1773	1773	1773
Increment	0	285	285	127	412	412
Staff						
IVUS guidance	119	137	154	2167	2185	2202
No IVUS guidance	130	110	89	1793	1773	1752
Increment	–11	27	65	374	412	450
Capital						
IVUS guidance	67	74	81	2178	2185	2192
No IVUS guidance	52	44	36	1781	1773	1765
Increment	–15	30	45	397	412	427

TABLE 51 *Results of scenario analysis for intervention cost calculation*

	Total intervention cost per patient (£)		
	Best	**Baseline**	**Worst**
IVUS guidance	1676	2185	2408
No IVUS guidance	2017	1773	1529
Incremental intervention cost	–341	412	879

TABLE 52 *Ranges of parameter values used for sensitivity analyses of the decision-analytic model*

	Restenosis rate			Systematic restenosis rate			MACE rate		
	Best	**Baseline**	**Worst**	**Best**	**Baseline**	**Worst**	**Best**	**Baseline**	**Worst**
IVUS guidance	0.09	0.13	0.16	0.36	0.50	0.64	0.02	0.04	0.06
No IVUS guidance	0.28	0.24	0.20	0.57	0.47	0.38	0.10	0.07	0.05

TABLE 53 *Results of one-way analysis for decision-analytic model*

	Costs per patient (£)								
	Restenosis rate			Symptomatic restenosis rate			MACE		
	Best	**Baseline**	**Worst**	**Best**	**Baseline**	**Worst**	**Best**	**Baseline**	**Worst**
IVUS guidance	214	281	331	220	281	342	249	281	313
No IVUS guidance	586	523	461	604	523	451	586	523	481
Increment	–372	–242	–130	–366	–242	–109	–337	–242	–168

TABLE 54 *Results of scenario analysis for decision-analytic model*

	Costs per patient (£)		
	Best	**Baseline**	**Worst**
IVUS guidance	140	281	438
No IVUS guidance	743	523	359
6-month incremental outcome cost	–603	–242	79

patient could range from a saving of £603 through a baseline saving of £242 to a cost of £79.

The probabilities and costs for the best-case scenario are shown on the decision tree in *Figure 6* and those for the worst-case scenario in *Figure 7*.

When the results of the scenario analysis on the decision model (for incremental outcome cost) are combined with the results for intervention costs, the total incremental cost per patient ranges from a saving of £944, through a baseline cost of £170 to a cost of £958. The $ICER_{re}$ = (total incremental cost per patient)/(absolute reduction in restenosis rate) ranges from a saving of £4968 through a baseline cost of £1545 to a cost of £23,950 per restenosis event avoided.

The effect of setting the TLR rate in the IVUS-guidance arm to 0.55 and that in the no-IVUS-guidance arm to 0.69,[105] while retaining baseline values for other parameters, was to change the incremental outcome cost from a baseline saving of £242 to a saving of £306. When the repeat PTCA rate in the no-IVUS-guidance arm was set to 0.75, while retaining baseline values for other parameters, the effect was to change the incremental outcome cost from a baseline saving of £242 to a saving of £213.

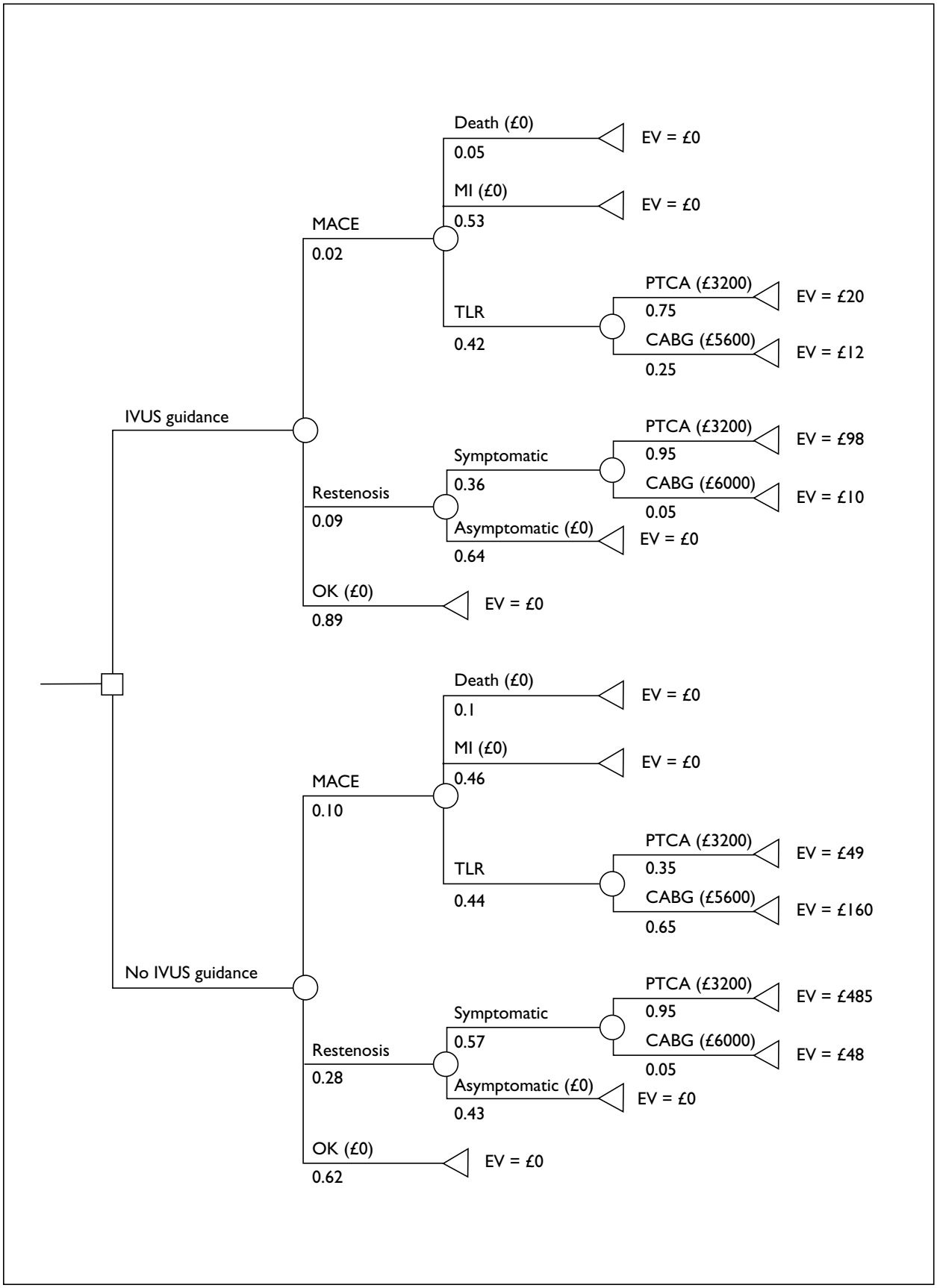

FIGURE 6 *Decision tree resulting from best-case scenario modelling. The outcome cost associated with the IVUS-guidance arm is £140 and the outcome cost associated with the no-IVUS-guidance arm is £743 (EV, expected value; □, clinical decision; ○, chance event; ◁, final outcome point)*

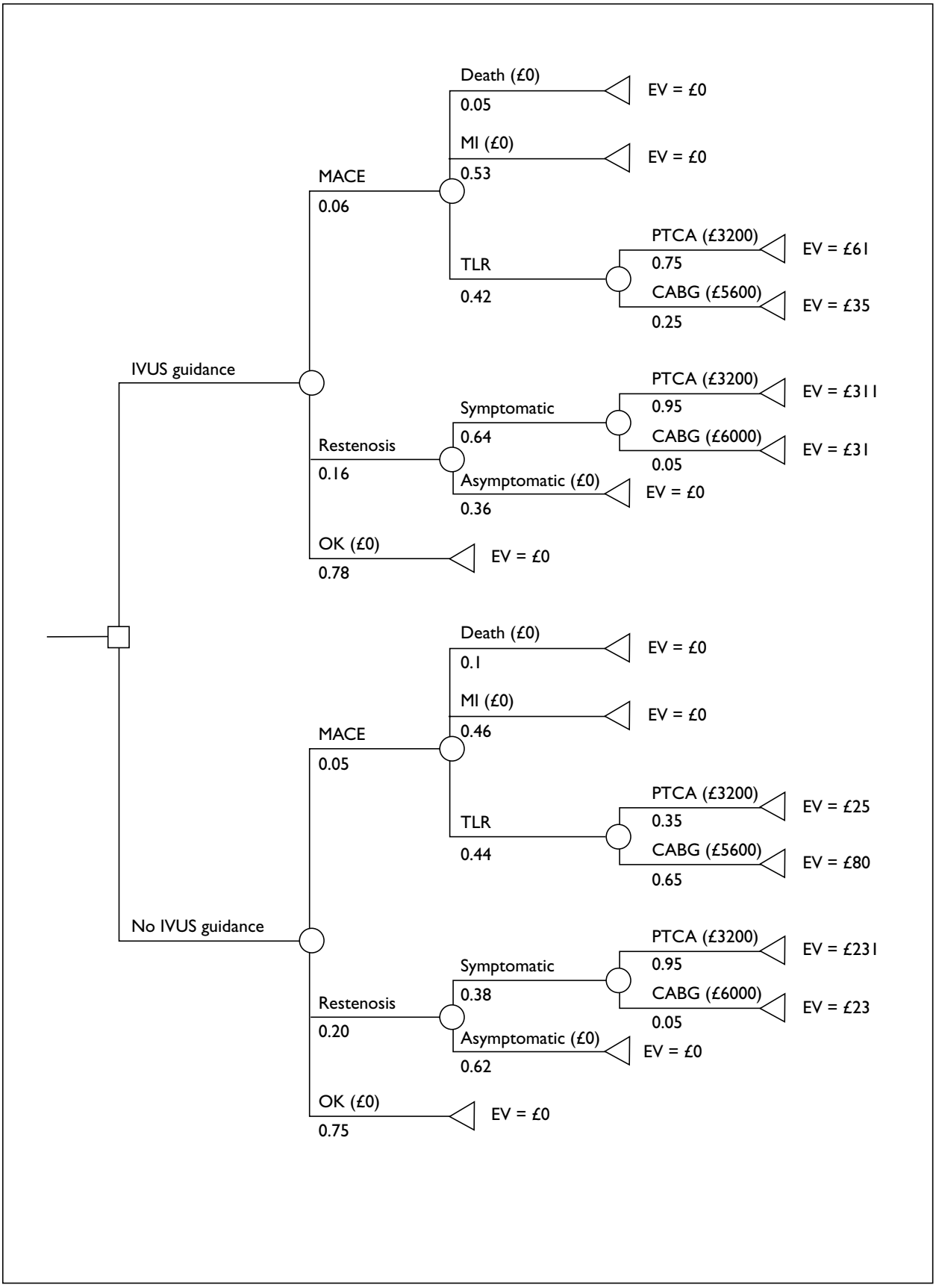

FIGURE 7 *Decision tree resulting from worst-case scenario modelling. The outcome cost associated with the IVUS-guidance arm is £438 and the outcome cost associated with the no-IVUS-guidance arm is £359 (EV, expected value; □, clinical decision; ○, chance event; ◁, final outcome point)*

Conclusion

Stenting with IVUS guidance is not the dominant technology compared with stenting without IVUS guidance, as it is more expensive in the worst-case scenario. Although it is more effective in the worst-case scenario, cost-effectiveness was not robustly demonstrated because the cost in that case was above the cost-effectiveness threshold. Nor can stenting without IVUS guidance be said to be dominant, as IVUS guidance is cheaper and more effective in the best-case scenario.

In the one-way analysis of the parameters of the decision model, the largest range of costs resulted from variations in the value of the symptomatic restenosis rate. It cannot be concluded that the model is robust, as the major parameters changed the resulting costs by up to £142. However, the effect of changes in the TLR rate and repeat PTCA rate in the MACE branches was small.

In chapter 6, results were presented that showed that IVUS-guided stenting will remain cost-effective (for a limit of £10,000 per QALY) if the absolute reduction in restenosis rate is above 0.07 or the total incremental cost per patient is under £264 (with the other variables held constant). If a baseline restenosis rate of 0.24 is set for non-IVUS-guided stenting (*Table 52*), then the worst restenosis rate that would still provide cost-effectiveness is 0.31. Jeremias and colleagues[137] reported a restenosis rate of 0.35 for IVUS-guided stenting, a rate that would make the intervention not cost-effective. Although this was a small study of 43 patients it did not include a higher percentage of patients with unstable angina or restenotic lesions than other articles. As this suggests that similar results are likely to be obtained by other workers, our conclusion is that the issue of cost-effectiveness is finely balanced.

From the one-way analysis of the intervention cost it can be seen that changes in the costs for stents and balloons have a bigger impact on the total cost than capital and staff costs. As the total incremental costs per patient must be kept below £264 for cost-effectiveness, a slight increase in the use of consumables could also prevent the intervention from being cost-effective.

Chapter 8
Discussion

This chapter is divided into three sections. First methodological issues associated with the literature review and decision-analytic model are covered, then the results of the review are discussed. The chapter concludes with an analysis of the changes in the knowledge base in the area covered by the review.

Methodology

Literature review

Search strategy

The search strategy was similar to those used in previous systematic reviews of medical imaging devices.[6,65] A low-precision search meant that only 1.7% of articles initially identified remained after the electronic, manual and final exclusion criteria had been applied. Although this appears to be a wasteful method of working, it is very effective in this field where searching for articles with a particular study design, such as for RCTs, is unproductive. The references, including their keyword and subject heading fields were downloaded into the Reference Manager database. As the initial search had been so inclusive and was designed to find all papers relating to the technology, this secondary database was then available for searches addressing further questions in the review, in this case those addressing reproducibility and IVUS-guided therapy for in-stent restenosis.

There is considerable overlap between the main databases. Of the initial retrievals, 44% were subsequently excluded as duplicates, and there was no source from which no unique retrievals were made (see *Table 5*). In this case, once the final exclusion criteria had been applied, no references found only in Compendex or Page 1 remained. The distribution between MEDLINE, EMBASE and BIDS (Science Citation Index and Index to Scientific and Technical Proceedings) was 70%, 13%, 17%. Three relevant articles were found in Inside, three via the Internet, and contacting experts resulted in information on two studies.

Of the 17 articles included in the review of IVUS-guided interventions, 16 (94%) were from the three main electronic databases, MEDLINE, EMBASE and Science Citation Index, and of these 14 (88%) were in MEDLINE, 14 (88%) in EMBASE and all 16 were in Science Citation Index. The *Journal of Invasive Cardiology* was not listed on either MEDLINE or EMBASE, meaning that the article by Serruys and colleagues[143] would have been missed in a search of those databases. Similarly, the *Journal of Interventional Cardiology*[131] was not available on MEDLINE, and *Catheterization and Cardiovascular Interventions*[137] was not available on EMBASE.

The search strategies used did not find every relevant article held in each database. Only 12 of the 14 articles (86%) listed in MEDLINE were retrieved by our search. Of the 14 (93%) listed in EMBASE, 13 were retrieved by the search. However, the search successfully identified all 16 articles listed in Science Citation Index. One article[134] published in *Circulation* was missed by the searches of both MEDLINE and EMBASE, because there were no IVUS-specific words in the title or abstract. The BIDS search strategy was successful in this case because a relevant word had been included in the keyword field, while the relevant MeSH term had not been used for indexing in MEDLINE and EMBASE. A second article from *Circulation*[133] was also missed in the search of MEDLINE because text words were absent from the title and abstract, and the expected MeSH heading had not been allocated. In this case, however, appropriate keywords had been allocated in both EMBASE and BIDS.

The seventeenth article[105] included in the review was identified by contacting experts in the field.

A number of potentially useful journals were identified but they were not readily available and so were not handsearched (see *Table 13*). The likelihood of missing an important primary source is believed to be low. The impact on the final results, even if an article was missed, is also likely to be small because there was much uncertainty from lack of information and very heterogeneous sources. The conventional wisdom[66] of systematic reviewing and meta-analysis demands an exhaustive search but work is needed to quantify how exhaustive a search need be when information quality is very low.

Although structured and systematic reviews are now being commissioned by a number of bodies, dissemination of the results is sometimes inadequate. A valuable resource for this review was a DEC report commissioned by the South East Regional Research & Development Directorate of the NHS. The report was not listed in any electronic index, including the Cochrane Library, but is readily available from the DEC website.[67] In the future, corresponding resources will be available from the National Institute for Clinical Excellence.[268]

Inclusion criteria

In the review of IVUS-guided interventions, the inclusion criteria were entirely subject-based. Criteria based on study design, such as those that would have allowed inclusion only of RCTs, were not used because of the possibility that no articles would satisfy the criteria. The situation was slightly different for the control arm, where studies about PTCA and stenting were sought without demanding any image-guidance. RCTs do exist in this area, and it was possible to set inclusion criteria that limited the search to RCTs and systematic reviews only.

The strict 10-point health economics criteria developed by Drummond and colleagues[71] were not used but no articles were identified, even with much less restrictive criteria. This shortage of health economics evidence has been noted by reviewers in related clinical areas[269] and in other areas of medical imaging.[6,65]

Relevance and validity

Articles were not excluded on grounds of validity; the effect this may have had on the results of the review are discussed below. The most prevalent threat to validity was selection bias, with many of the articles presenting findings from relatively low-risk patient groups. Several articles had high incidence of loss to follow-up, which was not adequately explained. The second important variation between articles was in their definition of 'IVUS optimisation' of stent deployment. Since the MUSIC study,[44] the MUSIC criteria (see appendix 1) have become the *de facto* standard but in earlier work there were differences. It was decided not to perform any subgroup analysis, as so few articles were included.

Data extraction

Extracting data from the articles was difficult because much of the information required for modelling represented intermediate event rates that were not of concern to the authors of the primary articles. It was necessary for three readers to reach a consensus regarding each article but this had the advantage of minimising the risk of bias being introduced into the review by using a single reader. Limitations in the published articles included the recording of hierarchical endpoints, so that only the worst event for each patient was included, not all the events preceding it. Complication rates would be reported, and also later events, but without an indication about the event rate for the subgroup with complications. This type of detailed information is essential for accurate modelling.

Data synthesis

Minimal data synthesis was possible because of the heterogeneity of the included articles.

Decision-analytic model

The decision tree that was agreed by the panel to be the basis for modelling was, to some degree, a compromise. A tree giving an accurate representation of current UK clinical practice would have been difficult to populate with data from the literature. Furthermore, even when a tree was developed that was consistent with the literature, it was necessary to simplify it further because information about intermediate steps could not be obtained. An example of this occurs early in the tree. In the decision tree used (see *Figure 2*), the IVUS-guidance arm divides straight into three outcome branches. Ideally, there should have been a further four decision points before the outcome branches, representing equipment availability, success in crossing the lesion, achievement of IVUS-optimisation of stenting, and further adjunct procedures. Expert clinical opinion was of value in helping decide which decision points were important enough to retain. Omission of a decision point is equivalent to the decision being the same for all subjects. If the clinical experts deemed a decision point important but no data were available from the literature to assign a probability split, then a range of values suggested by the experts would be applied. However, there were no decision points of this type in our tree.

No cost was assigned to the outcome of MI. Had such a cost been included it would have reduced the apparent costs of using IVUS guidance. The cost should be included in future development of the model but, as the evidence at present is not strong, it was decided to discount the effect. While these events undoubtedly give rise to healthcare costs, the potential variability is large according to the precise circumstances of the

event and the management given or attempted. No indication of such management is given in the published studies. Rather than make unsupported assumptions, it was decided to adopt a conservative approach and not include costs for these events in the analysis, thereby excluding a source of potential cost advantage in the IVUS branch. A major concern over including costs for these events was the 6-month time horizon imposed on the analysis by the availability of reliable clinical outcome data. The small differences in the probability of death and MI between the branches might well disappear over an extended period.

If the difference proves to be durable in the longer term, then the relative cost of IVUS use will be greatly reduced, also reducing the cost/QALY ratio. The view was taken that it would be more appropriate to look at a more restricted cost comparison in the first instance. If IVUS showed cost-effectiveness in this, then the inclusion of costs for MI and death would enhance this. If the cost-effectiveness of IVUS proved to be marginal, then further work to include reliable estimates of the additional event cost would be justified.

The shortage of cost-effectiveness data in radiology is well known,[270] and it was necessary to draw cost data from local sources[79] and from non-imaging literature.[77] The procedural time used came from a local catheterisation laboratory management database, which is compiled by nursing staff. The time recorded represents the total time spent by a patient in the laboratory. Although this time is greater than that for the interventional procedure itself, the analysis was based on the incremental time of adding IVUS guidance to a procedure, and an estimate of time made in this way will represent the maximum increment in procedural time that could be expected. Additionally, the local study from which the values for intervention cost were derived may have been unrepresentative of the groups receiving IVUS guidance in the published articles. They were not randomly referred for IVUS guidance and a degree of clinical judgement was involved in their selection. This suggests that their clinical status may have been more complicated than average. Additionally, the study did not reflect contemporary practice, so the estimates of procedural time and balloon use, and the associated costs, are likely to be too high. The study involved a stepped approach to high-pressure stent deployment, in which pressures of 9, 12 and 14 atmospheres were used, with IVUS after each stage and a second balloon used. A more representative model would have been to deploy the stent at high pressure and then use IVUS to assess the adequacy of the deployment. This would have given a smaller difference between the procedure time for the groups with and without IVUS guidance. Our model may therefore represent the use of IVUS guidance in the hands of the inexperienced and we are confident that it is not overemphasising the benefits of IVUS.

In the absence of detailed information on the nature of revascularisation procedures from the included studies, assumptions had to be made. When symptomatic restenosis is diagnosed without immediate need for intervention, subsequent revascularisation can be planned and can therefore be regarded as elective. In the case of MACE, revascularisation events that take place without prior classification as symptomatic restenosis are MACE events. It is therefore highly likely that such interventions are urgent and can be regarded as emergencies. As reported by McKenna and colleagues[77] published studies consistently show that emergency CABG procedures cost less on average than elective CABG. This is because they either follow the failure of other interventions and some preparatory steps have already been conducted, or they are initiated in haste without the preliminary clinic visits that might be included in the cost of an elective procedure. The assumptions made in the model are therefore biased against the IVUS branch (as more of the less-expensive emergency CABG events occur in the non-IVUS-guidance branch). This conservative approach is standard practice in modelling, in the absence of definitive data.

The cost differences are not great, however, with emergency CABG being some 7% less expensive. If all CABG procedures were costed at the elective rate, the cost difference in favour of the IVUS branch would increase by £7. If all CABG procedures were costed at the emergency rate, the cost difference in favour of the IVUS branch would reduce by £2.

An assumption was made regarding equal capacity to treat all the patients undergoing IVUS guidance. IVUS guidance quite conceivably could increase the procedure time that would lead to a reduction in patient throughput or the need to add new facilities. The former option increases waiting times and could increase the rate of adverse events, while in the latter the associated costs must be included in the analysis. Similarly, the analysis did not include the cost implications of a failed attempt at using IVUS guidance, increased consumables usage arising from attempts to achieve IVUS optimisation or minor

complications such as dissections. Indirect effects on society of reducing restenosis, and so possibly affecting future healthcare consumption, were not taken into consideration in the analysis.

A threat to the external validity of the model arose from the problems associated with properly costing the equipment. It was not possible to determine the actual price of the equipment because currently it is supplied as part of a contract for catheter supply. Cost was estimated for the model, but it is not known how close the estimate will be to the price charged once the technology has become sufficiently ubiquitous to be sold independently.

Only the intermediate, or surrogate, outcome[271] of restenosis rate at 6 months was available from the published literature. It was necessary to extrapolate to get an estimate of longer-term benefit in terms of quality of life, and this was done by estimating the QALY gain per restenosis event avoided from a published article[85] on the benefits of stenting. It was assumed that this gain would be the same, whatever way in which the reduction in restenosis rate was achieved. This may not be a valid assumption. For example, the mechanism of revascularisation may be different in PTCA alone and PTCA with stenting,[46,272] and so the mechanism of restenosis may differ too. Such a difference would affect long-term outcome. The limited modelling undertaken here is based on the most reliable data, which is restricted largely to 6 months of follow-up. The actual benefit from preventing or delaying MACE accrues over the patient's lifetime, well beyond the scope of most clinical trials. To project the future gains in survival, quality of life and cost-savings requires an epidemiological model of the relative risks of MACE for patients treated in different ways. Such models have been created and used for the evaluation of stenting *per se*.[85] Given the limited data on IVUS, and the uncertainty over its best method of deployment, the creation of a long-term model was not considered appropriate at this point. Once the data on the short-term impact of IVUS are more reliable, then more formal long-term analysis could be undertaken by adapting an existing model or creating a new one.

Although the study used for extrapolation[85] was carried out in the USA, it used an established cardiovascular risk model and used sound methodology. Clearly, information from several studies using UK patient preferences would have been preferable but, at the time the work was carried out, no such studies were available.

A priori, there is no reason to expect major differences in the health state preferences of patients from the USA and UK, so the data from Cohen and colleagues[85] should give a reasonable indication of the potential health gain.

The extrapolation used the cost differences between the IVUS-guidance and no-IVUS-guidance branches from the 6-month analysis and projected differences in QALYs using the restenosis rate at 6 months. Because the Cohen model[85] used American data, it was not possible to extrapolate the costs. This was a conservative approach as a delayed or reduced pattern of long-term cardiovascular events in the IVUS branch is likely to lead to further relative cost reductions. Favourable results from this restricted extrapolation would indicate the need for further research to confirm the appropriateness of the preference data in the UK context. Unfavourable results would indicate the need for confirmation of the preference data and a more detailed analysis of costs in the post 6-months period.

The addition of IVUS will increase the immediate costs of a procedure but this is likely to be offset by avoidance of repeat procedures. Further cost offsets may result from a reduction in the MACE rate. However, in the longer term, most patients are likely to suffer a further cardiovascular event so that the cost of future MIs will not be avoided, just delayed. As costs will be discounted, the delay in major cost items will lead to an overall cost reduction in present value terms but this may not produce an overall net cost saving to the NHS from using IVUS. Delayed restenosis and MACE will produce quality-of-life and survival benefits to patients, so that even if it does not produce net cost savings, IVUS may produce health benefits in a cost-effective way.

The use of £10,000 as a cost/QALY decision threshold was somewhat arbitrary. There is no conceptual or empirical justification for this figure. It has been frequently used as a rule of thumb in discussion; for example, a recent article[273] stated that, "In the United Kingdom, costs for treatments of less than £5000/quality-adjusted life year (QALY) are perceived as highly cost effective, whereas those over £10000/QALY are considered expensive." A higher figure, for example, of up to £20,000, may be considered applicable if the evidence is stronger.[274] The use of any threshold can be challenged by the observation that although many common interventions cost less than £10,000 per QALY, some costing more are used routinely.[275] Examples are shown in *Table 55*.

TABLE 55 *Costs per QALY[276] for various procedures in the UK, updated to 1999 using the* UK Hospital and Community Health Services Index[277]

Procedure	Cost per QALY (£)	
	1990 prices	1999 prices
Anti-hypertensive therapy to prevent stroke (age 45–64 years)	940	1,296
Pacemaker implantation	1,100	1,516
Hip replacement	1,180	1,627
CABG (left main vessel disease)	2,090	2,881
Kidney transplantation	4,710	6,493
Breast cancer screening	5,780	7,968
Heart transplantation	7,840	10,808
Home haemodialysis	17,260	23,794
CABG (single-vessel disease)	18,830	25,958

Although the model was not particularly sensitive to changes in the time required for a procedure, it can be suggested that diffusion of a technology can be enhanced by developments that reduce the additional procedure time required. An example in this area would be the integrated catheter, 'ICUS on a balloon'.

The initial design and population of the model was a lengthy process but, now that it exists, it will be relatively quick and inexpensive to update. In particular, additional evidence about restenosis rates from new studies should increase the robustness of the model by reducing the associated CIs. Similarly, the patients involved included all age ranges and future modifications should concentrate on specific age groups, especially if extrapolation to long-term outcome is to be performed. It may be possible, as the knowledge base increases, to apply validity-based inclusion criteria, which should also increase robustness.

Results of the review

IVUS-guided interventions

Of the studies included, none was sufficiently well designed or performed to return clear evidence on what would appear to be a simple question: if IVUS-guided stent deployment results in statistically larger stent minimal luminal dimensions, then does this translate into reduced restenosis rates? The most rigorously designed study[142] was underpowered. The CRUISE study[105] was promising, but fundamentally restricted by the necessity to avoid influencing the primary randomisation of the STARS trial. The use of IVUS was assigned on a centre-by-centre basis. In addition, its outcomes were measured as revascularisation rates and not as angiographic restenosis rates. Nonetheless, the results of these studies, and those of the others, does support the hypothesis of a reduction in restenosis with IVUS guidance but the evidence may not be described as strong.

There were some noticeable contrasts in reported restenosis rates, particularly the low rate of the MUSIC study[44] and the high rate reported by Jeremias and colleagues.[137] This is likely to be related to the baseline characteristics of the patient groups, which were incompletely reported in the latter. The MUSIC study excluded patients with unstable angina and the group comprised relatively low-risk patients. Determination of angiographic restenosis demands follow-up angiography. However, not all patients agree to follow-up angiography and it is likely that those who do not are asymptomatic. So the completeness of angiographic follow-up affects the apparent incidence of restenosis, and angiographic restenosis may overestimate the true restenosis rate. The OPTICUS[104] trial has not yet been published but promises useful results.

There is even less primary evidence about longer-term follow-up and quality of life. The decision-analytic model did not give conclusive results. It showed that IVUS-guided stenting is not dominant over non-IVUS-guided stenting but it may be cost-effective in certain circumstances. The model was sensitive to changes in restenosis rate and consumables costs. Thus there is a need for confirmation of the preference data and more detailed analysis of costs in the post-6-months period.

The probability data acquired for the model implied that the method of target lesion

revascularisation after MACE following stenting was different for the IVUS-guidance and non-IVUS-guidance arms. In the former, 25% of the procedures were CABGs, while in the latter 65% were CABGs. It would be unwise to draw conclusions. At this point in the decision tree, the numbers of patients are small and the CIs wide. For example, the CI for the 25% figure runs from 0% to 55%. In addition, the result is counter-intuitive. When there is no information from IVUS, a higher rate of repeated PTCA would be expected than in the IVUS-guidance group, in which more information about the quality of stent deployment is available.

The decision model reflects the current approach by the vast majority of interventional cardiac centres who perform PTCA with the intention to stent, and IVUS guidance is used to optimise the stent deployment. There are three alternative protocols that are coming into practice and remain untested in both clinical and economic terms. First, there is an important hypothesis that angioplasty alone, guided by IVUS, might be equally as efficacious as stenting. The opportunity to test this hypothesis has now passed, however, in the UK at least, with the publication (while this monograph was being refereed) of guidelines[278] from the National Institute for Clinical Excellence. In its 'Guidance on coronary artery stents in the treatment of ischaemic heart disease', it is stated that: "For patients with either stable or unstable angina, or acute myocardial infarction (MI) and where percutaneous coronary intervention (PCI) is the clinically appropriate procedure, stents should be used routinely." Second, the use of a high-pressure strategy without IVUS guidance has led to low sub-acute thrombosis rates being reported;[279] this suggests that the stenting protocol developed with the help of IVUS may no longer need IVUS guidance to be effective. To date, no study has been designed specifically to determine whether optimisation of stenting with IVUS rather than angiography results in measurable differences in acute or subacute thrombosis. The frequency of the event is of the order of 1%, so a much larger study than any undertaken to date would be required. Third, IVUS may be used to plan the intervention and determine whether or not a stent is required. Vessel dissection after angioplasty increases the risk of acute complications, yet such complications are still relatively rare even when evident on angiography. This suggests potential cost savings from reduced stent usage[63] but a rigorous trial of IVUS planning versus angiographic planning is needed. As more centres move to using IVUS in these ways, it will be important that such evidence is obtained.

Developments in the techniques of interventional cardiology may impact on the future role of IVUS. A strategy of direct stenting is increasingly being used. This involves stent deployment without any pre-dilation, although high-pressure inflation may be used post stenting. In this situation, IVUS can only be used post stenting to assess the success of the deployment but is not used before stenting to size balloons and stents. The technique is being rapidly adopted but there is currently no evidence on its effectiveness. Rapid adoption of new niche applications is likely in the future: this field is one where careful horizon scanning will be important.

In-stent restenosis

Although no articles were included about IVUS-guidance therapy for in-stent restenosis, there is a large amount of literature on the mechanism.[170,239,280] Restenosis after PTCA tends to result from geometric arterial remodelling,[140] while in-stent restenosis appears to be solely caused by neointimal proliferation. IVUS has theoretical advantages over angiography in identifying non-calcified eccentric plaque that should be better dealt with by DCA and, in identifying calcium, that would lead to a choice of ROTA.

Reproducibility

The studies fell into two categories: those designed to investigate reproducibility[114,120,122] and those in which a subset of the images acquired as part of a larger investigation were measured more than once. Few of the study designs for measuring intra-observer variability satisfied the requirement that measurements should be made on different images. This was specified because, when the same image is used, an over-optimistic estimate of reproducibility is obtained. These results appear in *Table 29*. The results from the two studies that did satisfy all the inclusion criteria[114,115] were in good agreement. Changes in area over 1.6 mm^2 may be taken to be genuine changes, not artefacts of measurement. The standard criteria for assessing stent deployment are those specified in the MUSIC study[44] (see appendix 1). In particular:

- in-stent minimal lumen area of at least 90% of the average reference lumen area or at least 100% of lumen area of the segment with the lowest lumen area. In-stent lumen area of proximal stent entrance at least 90% of proximal reference lumen area. If the in-stent lumen area > 9.0 mm^2, then in-stent minimal lumen area at least 80% of the average

reference lumen area or at least 90% of lumen area of the reference segment with the lowest lumen area.

For in-stent lumens under 9.0 mm^2, it must be possible to measure a 10% difference in lumen area, an area of the order of 1 mm^2. For in-stent lumens over 9.0 mm^2, the measurable difference is 20%, an area of the order of 2 mm^2. The value of 1.6 mm^2 suggests that adequate assessment may be made using IVUS only for the larger in-stent lumens.

Interobserver variability was greater than intra-observer, which is unsurprising. This suggests that when repeated measurements are made during an intervention to determine when a stent has been optimally deployed, the same observer should ideally make each measurement. Similarly, longitudinal measurements, to track in-stent restenosis, for example, would be better made by one observer.

It was notable that the interobserver variability was greater for automated than for manual border definition. This may be partly a result of the differing sizes and compositions of the study groups, and may also reflect the way in which the image to be measured was chosen in each study. A study would need to be performed that made conditions as similar as possible for both methods of border definition, before any firm conclusions could be drawn about their relative merits.

Ideally, results of outcome studies would be available to determine if a technology was having any impact but reproducibility measurements can give guidance at an early stage. For example, in this case, if reproducibility was so poor that changes in area necessary for a clinical decision could not be detected, then it could be predicted that impact on patient outcome would be small. More appropriate applications could be pursued or changes made in the methodology.

Other

In this review one important application of IVUS has not been addressed. Angiographically normal segments of artery may manifest changes of coronary atheroma within their walls and the apparently normal artery adjacent to a significant lesion is often heavily diseased. At post mortem it is apparent that the tissue characteristics of plaques vary considerably. Some are predominantly fibrous plaques with smooth muscle cell proliferation, others have heavily lipid-laden cores, and still others contain significant amounts of calcification. These differences may not be apparent on angiography and may be better appreciated by IVUS. Angiography is poor at assessing lesion calcification.[282] Indeed, where visual assessment by angiography proves to be wrong it is often because of the presence of calcification. It has been reported that angiography detects calcification about half as often as ICUS.[282] This is potentially important because Ca2+ is an important determinant of dissection following balloon angioplasty[283–285] and limits the success of DCA,[286] whereas extensive subendothelial calcium can be removed by ROTA.[287]

Changes in the knowledge base

Seven trials[44,115,137-139,142,143] on IVUS stenting published between 1997 and 1999 were included in the review of outcome at 6 months. They represented work undertaken since 1993. Four unpublished trials involving IVUS-guided stenting were identified from the search of the Internet or from contacting experts in the field. The OPTICUS trial[104] is reported as complete by the National Research Register but was unpublished at the time of writing (September 1999). An article on the SIPS trial is under peer review. Two further ongoing trials[102,103] were identified from the National Research Register and are scheduled for completion in 2001 and 2005.

For this review, very little evidence was found on IVUS-optimised PTCA or on other IVUS-guided interventions such as DCA and ROTA. A search was made of Index of Scientific and Technical Proceedings, limited to 1998, to identify studies under way. Four major IVUS-guided stenting studies,[288–291] three IVUS-guided PTCA studies[292–294] and one general IVUS-guided intervention study[295] were identified. There were no articles relating to IVUS-guided DCA or ROTA.

Overall, there appears to be a fairly steady, but not rapid, rate of additions to the knowledge base, and an update of this review would be justified in less than 5 years.

Chapter 9
Conclusions

Implications for healthcare

None of the studies included in the review was sufficiently well designed or performed for there to be any implications for reducing restenosis in clinical practice.

Recommendations for further research

- An adequately powered, well-designed RCT that compares the long-term outcomes of stenting, with and without IVUS guidance, should be undertaken.
- An RCT to compare acute and subacute thrombosis rates and long-term outcome of high-pressure stent implantation strategies with and without IVUS guidance should be performed.
- An RCT to compare the long-term outcome of therapy guided by IVUS against the 'intention-to-stent' approach using angiographic guidance should be undertaken.
- There is a need for studies of cost and cost-effectiveness, based on the results of the RCTs suggested above, which follow guidelines for the measurement and valuation of costs.
- There is a strong case for a prospective audit to commence as soon as possible, along clearly defined lines that address the gaps in currently available data, of all stenting procedures carried out in the UK.
- The decision model presented here should be updated when results are available from trials currently in progress.
- The model should be revised to include alternative short-term endpoints.
- Monitoring of expert opinion (horizon scanning) is needed to identify future roles for IVUS, and early implementation of adequately powered RCTs to test the emergent applications. These might include IVUS guidance for high-risk, diffuse lesions in small vessels; novel delivery platforms; IVUS guidance of direct stent deployment.
- Measures to facilitate modelling are recommended. These would include support for supplementary data to be held on web servers, and routine collection of registry and local data. The development of guidelines to authors about the style of data presentation necessary is also indicated, as specific information about the treatment and outcome for subgroups is often difficult to extract.
- A structured review of the therapeutic and outcome impact of using IVUS to detect calcification and eccentric lesions is recommended, although based on the experience of the current review it is recognised that strong evidence that would be of use to decision-makers will not be found.

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Appendix 1
Definitions

CCS grades

This functional grading of stable angina pectoris was developed by the Canadian Cardiovascular Society (CCS). The grade indicates the physical efforts that produce angina.[296]

Grade 1: Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation.

Grade 2: Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when 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.

Grade 3: Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions.

Grade 4: Inability to carry on any physical activity without discomfort – anginal syndrome may be present at rest.

Lesion specific characteristics

These are defined in the American College of Cardiology/American Heart Association Task Force Report, *Guidelines for percutaneous transluminal coronary angioplasty.*[297] The gradings can be used to predict the risk of interventional procedures.

Type A lesions (minimally complex)

- Discrete (length < 10 mm)
- Concentric
- Readily accessible
- Non-angulated segment (< 45°)
- Smooth contour
- Little or no calcification
- Less than totally occlusive
- Not ostial in location
- No major side-branch involvement
- Absence of thrombus

Type B lesions (moderately complex)

Type B1 lesions have one B characteristic; type B2 lesions have two or more B characteristics.

- Tubular (length 10–20 mm)
- Eccentric
- Moderate tortuosity of proximal segment
- Moderately angulated segment (> 45°, < 90°)
- Irregular contour
- Moderate or heavy calcification
- Total occlusions < 3 months old
- Ostial in location
- Bifurcation lesions requiring double guide wires
- Some thrombus present

Type C lesions (severely complex)

- Diffuse (length > 2 cm)
- Excessive tortuosity of proximal segment
- Extremely angulated segments > 90°
- Total occlusions > 3 months old and/or bridging collaterals
- Inability to protect major side branches
- Degenerated vein grafts with friable lesions

MUSIC criteria

The MUSIC (Multicenter Ultrasound Stenting In Coronaries study) criteria have become the standard for defining stent optimisation.[44]

- Complete apposition of the stent over its entire length against the vessel wall.
- In-stent minimal lumen area at least 90% of the average reference lumen area or at least 100% of lumen area of the segment with the lowest lumen area. In-stent lumen area of proximal stent entrance at least 90% of proximal reference lumen area. If the in-stent lumen area > 9.0 mm^2, then in-stent minimal lumen area at least 80% of the average reference lumen area or at least 90% of lumen area of the reference segment with the lowest lumen area.
- Symmetrical stent expansion defined by the ratio of the minimum to maximum luminal diameter of at least 0.7.

Appendix 2

Search strategies

The abbreviations and commands used in electronic search strategies are given in *Table 56*.

IVUS-guided interventions

MEDLINE

1. exp ultrasonography/
2. ultraso$.af
3. sono$.ti,ab,hw
4. ultra-so$.ti,ab,hw
5. 1 or 2 or 3 or 4
6. intravascular.ti,ab,hw
7. intracoronary.ti,ab,hw
8. endovascular.ti,ab,hw
9. endocoronary.ti,ab,hw
10. intra-vascular.ti,ab,hw
11. intra-coronary.ti,ab,hw
12. endo-vascular.ti,ab,hw
13. endo-coronary.ti,ab,hw
14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 5 and 14
16. ivus.ti,ab
17. cvis.ti,ab
18. sonicath.ti,ab
19. 15 or 16 or 17 or 18
20. icus.ti,ab
21. (intensive care adj3 unit).ti,ab
22. icu.ti,ab
23. 20 not (21 or 22)
24. endoluminal.ti,ab,hw
25. endo-luminal.ti,ab,hw
26. 24 or 25
27. 26 and 5
28. coronary.ti,ab,hw
29. 27 and 28
30. 19 or 23 or 29

EMBASE

1. exp echography/
2. echograph$.ti,ab,hw
3. ultraso$.ti,ab,hw
4. ultra-so$.ti,ab,hw
5. sono$.ti,ab,hw
6. 1 or 2 or 3 or 4 or 5
7. intravascular.ti,ab,hw

TABLE 56 *Commands and abbreviations used in electronic search strategies*

Abbreviation or command	Definition
$	Truncation symbol for MEDLINE and EMBASE
*	Truncation symbol for BIDS, Cochrane, Inside and Reference Manager
adj	Adjacent command for MEDLINE and EMBASE
#	Wild word command for BIDS
exp	Explode command for MEDLINE and EMBASE
ti	Title command for MEDLINE and EMBASE
ab	Abstract command for MEDLINE and EMBASE
hw	Headword command for MEDLINE and EMBASE, i.e. a single word anywhere in a MeSH term
tka	Title, keyword, abstract command for BIDS
me	Subject heading for Cochrane
, + -	BIDS Boolean commands OR, AND, and NOT, respectively
" - "	In BIDS, the search engine does not ignore the hyphen; hyphenated words must be separately specified and enclosed in quotation marks to avoid confusion with the hyphen used for the Boolean NOT command
	In MEDLINE and EMBASE searches hyphens are ignored

NB: The search interfaces used in this review to access MEDLINE and EMBASE were from Ovid. BIDS covers SCI, ISTP, Compendex and Page One databases using the standard BIDS WWW interface

8. intracoronary.ti,ab,hw
9. endovascular.ti,ab,hw
10. endocoronary.ti,ab,hw
11. intra-vascular.ti,ab,hw
12. intra-coronary.ti,ab,hw
13. endo-vascular.ti,ab,hw
14. endo-coronary.ti,ab,hw
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 6 and 15
17. ivus.ti,ab
18. cvis.ti,ab
19. sonicath.ti,ab
20. 16 or 17 or 18 or 19
21. icus.ti,ab
22. (intensive care adj3 unit).ti,ab
23. icu.ti,ab
24. 21 not (22 or 23)
25. endoluminal.ti,ab,hw
26. endo-luminal.ti,ab,hw
27. 25 or 26
28. 27 and 6
29. coronary.ti,ab,hw
30. 28 and 29
31. 20 or 24 or 30

BIDS

1. ultraso*.tka
2. "ultra-so*".tka
3. sono*.tka
4. echograph*.tka
5. 1,2,3,4
6. intravascular.tka
7. intracoronary.tka
8. endovascular.tka
9. endocoronary.tka
10. "intra-vacular".tka
11. "intra-coronary".tka
12. "endo-vascular".tka
13. "endo-coronary".tka
14. 6,7,8,9,10,11,12,13
15. 5+14
16. ivus.tka
17. cvis.tka
18. sonicath.tka
19. 15,16,17,18
20. icus.tka
21. intensive care unit*.tka
22. intensive care # unit*.tka
23. intensive care # # unit*.tka
24. intensive care # # # unit*.tka
25. icu.tka
26. 20-(21,22,23,24,25)
27. endoluminal.tka
28. "endo-luminal".tka
29. coronary.tka
30. 5+29+(27,28)
31. 19,26,30

Cochrane Library

1. Ultrasonography*.me
2. ultraso*
3. 1 or 2
4. intravascular
5. intracoronary
6. endovascular
7. endocoronary
8. 4 or 5 or 6 or 7
9. 3 and 8
10. IVUS
11. ICUS
12. 9 or 10 or 11

Inside (British Library)

Title OR abstract OR keyword: intravascular ultraso* OR intracoronary ultraso* OR endovascular ultraso* OR endocoronary ultraso* OR IVUS OR ICUS

Reference Manager

Reproducibility

1. **Title OR abstract**: reproducibility OR reproducible OR precision OR variability OR variation OR intraobserver OR intra-observer OR intra observer OR interobserver OR inter-observer OR inter observer OR (observer AND agree)
2. **Keywords**: reproducibility OR reproducibility of results OR observer variation OR variability OR interobserver variability
3. 1 OR 2

In-stent restenosis

1. **Title OR abstract**: in-stent OR instent OR in stent OR (margin AND resteno) OR neo-intimal OR neointimal OR neo intimal
2. **Keywords**: in stent restenosis OR neointima*
3. 1 OR 2

Control arm

MEDLINE

1. stents/
2. stent$.ti,ab
3. 1 or 2
4. angioplasty/
5. exp Balloon dilatation/
6. ptca.ti,ab
7. balloon$.ti,ab
8. 4 or 5 or 6 or 7
9. 3 or 8
10. 9 and RCT filter
11. limit 10 to meta analysis
12. limit 11 to english language

Cochrane Library

1. myocardial revascularization*.me
2. stent*
3. ptca
4. balloon
5. angioplasty
6. 1 or 2 or 3 or 4 or 5

Appendix 3

The systematic search of the Internet

Some authors classify any search that was made via a connection to the Internet as an Internet search. This definition would include, for example, searches of databases such as MEDLINE, which can also be accessed in other ways. The search described here was for information available only by an on-line connection, or for databases other than the well-known bibliographic databases that had already been searched. Information gateways on the World Wide Web (*WWW*) and Copernic,[298] a meta-search engine, were used.

The following categories were defined for classification of data.

Level 1 Information gateways, large medical databases and medical search engines.

Level 2 More specific databases, indexes or journal listings

Level 2A Sites or databases related to the type of evidence required (e.g. systematic review)

Level 2B Sites or databases related to the research specialty (e.g. cardiology)

Level 2C Sites or databases related both to the type of evidence and the research speciality.

Level 3 Articles, references to articles or information assessed as having potential for inclusion in the review, and not previously located by searches of electronic bibliographic databases.

Keywords

Three types of keyword were defined (*Figure 8*) to group searches according to type of resource, type of evidence or research speciality. The keywords associated with each category, used both for searching and to help classify the information retrieved, were:

- type of resource: database, search, index, gateway, library
- type of evidence: systematic literature review, systematic review, evidence-based medicine, evidence based medicine, randomised controlled trial, randomized controlled trial, randomized trial, randomised trial, HTA, health technology assessment.

For research speciality these were further subdivided into keywords related to:

- anatomy (cardiology, cardiovascular, coronary)
- disease (coronary artery disease)
- technology (ultrasound, stent, catheterisation, catheterization).

Different combinations of the keywords, as indicated in *Figure 8*, allowed the search to be focused on the different levels defined above. In particular, the region on the Venn diagram labelled 6 represents Level 3 information.

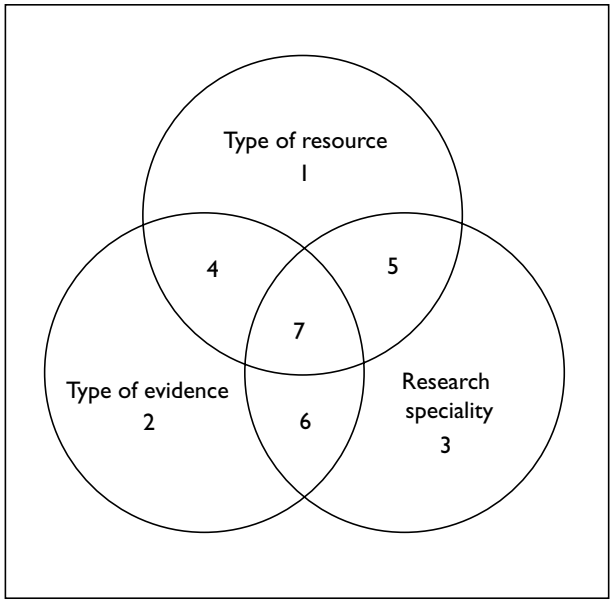

FIGURE 8 *Venn diagram showing how the different types of resource were found by combining keyword searches. Region 4 corresponds with Level 2A databases of the required type of evidence, region 5 with Level 2B databases in the required research speciality, and region 7 with Level 2C databases of both the required type and speciality. Region 6 corresponds with Level 3 results*

Further keywords used to focus on the topic of interest were:

- intravascular ultrasound, intracoronary ultrasound, IVUS, intravascular sonography, intracoronary, sonography, intravascular ultrasonics, intracoronary ultrasonics, intravascular, sonograph, intracoronary sonograph.

Use of these words allowed identification of Level 3 resources.

Gateway search

Level 1 sites were identified from existing knowledge, from the literature and from discussion groups. Large medical gateways were searched for further Level 1 sites via links or by using search facilities. A similar search was carried out using Copernic.[298] In both searches the keywords were those describing the type of resource.

Level 2 sites were identified from Level 1 sites both by conducting a site search and by browsing the site using the links provided, wherever possible. Links containing the relevant keywords were followed, together with those believed to be relevant by the searcher. For efficiency, a limit was put on the number of links followed. For inclusion a resource had to be found within five links of the Level 1 start page. Links in advertisements were ignored. Sites retrieved were then categorised into Level 2A, 2B or 2C.

Level 3 resources were identified from the three types of Level 2 site identified using different protocols. For Level 2A sites, a search based on the research speciality was conducted using the anatomy, disease and technology keywords. It was focused using the topic specific keywords. For Level 2B sites, a search using the type of evidence keywords was conducted, and focused using the topic specific keywords. For Level 2C sites, the topic specific keywords alone were used.

Copernic search

Copernic[296] is a computer program classified as a search agent. It can query multiple search engines, directories, news archives and email databases simultaneously. It removes duplicate listings and retrieves results for reading offline. A score is assigned to a site corresponding to the ranking given by the engines used, so there is no bias towards any particular engine. In this work, the software provided a quick and thorough method of searching a large part of the indexed Internet. The number of retrievals from eight of the major Internet search engines was recorded, along with the number of dead links. A list of the 100 highest scoring sites was compiled by Copernic from the lists of 300 highest ranked sites from each engine. The search strategy was designed to mimic that used when searching the gateways (*Table 57*) and allowed categorisation of results into the same levels.

TABLE 57 *Search strategy used in Copernic*

Category of search result	Keywords used	Search methods
Level 1	(a) Gateway, search, database (b) medical, surgical	OR components of (a) and (b) (a) AND (b)
Level 2A	Systematic literature review, randomised controlled trial, evidence-based	OR keywords
Level 2B	Ultrasound, cardiology, coronary artery disease	OR keywords
Level 2C	(a) Systematic literature review, randomised controlled trial, evidence-based (b) ultrasound, cardiology, coronary artery disease	OR components of (a) and (b) (a) AND (b)
Level 3	Intravascular ultrasound, intravascular ultrasonics, intravascular sonography, IVUS, intracoronary ultrasound, intracoronary ultrasonics, intracoronary sonography	OR keywords

Appendix 4

Checklists: IVUS-guided interventions

Three checklists were used. In each the user was asked to complete the table for the study groups defined in the article, using values as presented in the article. Values in articles were given in several ways, including absolute numbers of patients or lesions or as percentages. The user would note which convention was used. The aetiology checklist is presented below together with that for patient characteristics. Additional columns were provided for the user to add additional information to that given in the article.

Aetiology checklist

Article title:														
Author						Year:								
Study group	De novo or restenosis	Native	Ostial	Graft	Unstable or stable	Non-Q MI	MI	CABG	PTCA	Other	Single lesion	Multi lesion	N1	N2
1														
2														
3														
4														
5														

NB: N1, number of patients included in study: N2, number of lesions included in study

Patient characteristics checklist

Study group	Intervention	Age	Gender	LAD	LCx	RCA	LM	Other	Other	Other	Other	Other
1												
2												
3												
4												
5												

Outcome results were recorded in the third checklist. The rows labelled Time A and Time B allowed results to be recorded for more than one outcome. Examples included outcomes measured in hospital, postdischarge, at 1 month or at 6 months. Clinical event rates were completed according to the data presented in the article on a per patient or per lesion basis.

Outcome details checklist

		Group 1	Group 2	Group 3	Group 4	Group 5
Death	Time A Time B					
MI	Time A Time B					
Non-Q MI	Time A Time B					
CABG	Time A Time B					
PTCA Time B	Time A					
Dissection	Target vessel Patient					
Restenosis (angiographic)	Target lesion Patient					
Restenosis (clinical)	Target lesion Patient					
Repeat intervention						
Repeat vascularisation						
Abrupt closure						
Acute vascular complications						
Spasm						
Thrombus						
Other						
Number followed-up	Patients (P)† Lesions (L)†					

† These may differ from the total number included in a study

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We look forward to hearing from you.

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