Intravascular Ultrasound

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Assessment report

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The Medical Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared for the Medicare Services Advisory Committee by Kirsten Howard, Epidemiologist, Simon Eckermann, Health Economist, and Associate Professor Anthony Keech, Deputy Director, from The NHMRC Clinical Trials Centre, University of Sydney, with recommendations made by the MSAC Supporting Committee for IVUS. The report was endorsed by the Commonwealth Minister for Health and Ageing on 17 May 2002

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Intravascular ultrasound (IVUS) is the generic name for any ultrasound technology that is used *in vivo* within blood vessels. More specifically, intracoronary ultrasound provides the ability to image the coronary arteries from within the lumen with ultrasound. It can be used to determine the extent and composition of atherosclerotic lesions in coronary and peripheral vessels and can measure the burden of non-occlusive atherosclerosis prior to clinical events. In addition to its role in diagnosis and determination of the extent of vessel occlusion, IVUS has evolved into an adjunct to interventional cardiology, particularly in assessment of the appropriate placement of intracoronary stents.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the NHMRC Clinical Trials Centre was engaged to conduct a systematic review of literature on the coronary applications of intravascular ultrasound. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of Intravascular Ultrasound

Clinical need

Cardiovascular disease is Australia's greatest health problem. It kills more people than any other disease (accounting for 40% of all deaths) and its health and economic burdens exceed that of any other disease. In 1993-94, cardiovascular disease accounted for the largest proportion of health system costs in Australia, $3.7 billion or 12% of total health system costs (Mathers & Penm 1999). Cardiovascular disease accounted for 2% of disease burden in Australia in 1996, 33.1% of premature mortality and 8.8% of years of equivalent 'healthy' life lost through disease, impairment and disability. Coronary heart disease accounts for almost 57% of the cardiovascular disease burden (Mathers, Vos, & Stevenson 1999).

In 1998–99, there were 158,131 hospitalisations where coronary heart disease was the principal diagnosis (3% of all hospitalisations and 36% of hospitalisations for cardiovascular disease). Acute myocardial infarction accounted for 33,908 hospitalisations in 1998–99, 21% of hospitalisations for coronary heart disease.

In 1998, there were 17,448 coronary artery bypass graft operations (Australian Institute of Health and Welfare 2000b). Over the same time there were 18,094 percutaneous transluminal coronary angioplasty (PTCA) procedures performed in Australia. Of these PTCA procedures, 14,838 (82%) patients also had stent placement during the procedure.

Safety

Overall, IVUS appears to be a relatively safe procedure. Adverse events appear to relate primarily to vasospasm which can be readily treated with intravenous nitrate therapy. The rate of major acute procedural complications associated with (but not necessarily caused by) IVUS, such as dissection or vessel closure, has been reported to be approximately <0.5%, with major complications more likely to occur in patients undergoing therapeutic IVUS rather than diagnostic IVUS imaging. Long-term safety information based on prospective one-year safety data from serial quantitative angiography in cardiac transplant recipients indicates that IVUS does not accelerate the progression of angiographically quantifiable disease, and that it also appeared to be safe for the evaluation of patients not undergoing interventional procedures.

Effectiveness

Diagnostic applications

IVUS appears to offer additional and complementary information over that provided by coronary angiography. It is able to more accurately demonstrate the likely extent of lesions in both coronary and peripheral vessels. It appears to have good sensitivity and specificity for detection of plaque dissections and media rupture, but lower sensitivity for the detection of plaque rupture and thrombus formation. It appears to have quite high accuracy in predicting the likely functional severity of lesions. IVUS can also provide information on the composition of plaques. There is some evidence to suggest that selected IVUS parameters may be able to predict clinical events.

There is some evidence that IVUS alters management of patients with angiographically indeterminate or ambiguous lesions. In other patient groups, it is reasonable to assume that if IVUS can more accurately determine the extent of lesions, then the treating physician can choose more appropriate therapy.

Therapeutic applications

Based on randomised controlled trial evidence, stent placement using IVUS guidance results in a statistically significant reduction in the odds of patients requiring target lesion revascularisation procedures at 9-12 months in the IVUS guided compared to non-IVUS guided treatment groups (Odds Ratio (OR) 0.73, 95% confidence interval 0.54 – 0.99, p=0.04). It should be noted that the upper limit of the 95% confidence interval is approaching the point of no effect (OR = 1). It is unclear at this stage whether the reduction in target lesion revascularisation is sustained over a longer follow-up period. It is also unclear whether it will result in improvements in either Q-wave myocardial infarction or in survival, as the trials were not powered to detect significant differences in either of these parameters.

Cost effectiveness

Using published randomised controlled trial evidence, the baseline cost per clinically-driven target lesion revascularisation prevented from IVUS guided stent deployment is estimated to be approximately $26,000 per target lesion revascularisation (TLR) prevented. This estimate varies from approximately $12,000 to approximately $800,000, per TLR prevented over the evidence based ranges examined in sensitivity analyses. In general the estimate of cost effectiveness remains highly sensitive to estimates of IVUS effectiveness.

Recommendation

Since there is currently insufficient evidence pertaining to the effectiveness and cost-effectivness of intravascular ultrasound as either a diagnostic or therapeutic tool, MSAC recommended that public funding should not be supported at this time for this procedure.

- The Minister for Health and Ageing accepted this recommendation on 17 May 2002 -

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of intravascular ultrasound, which is both a diagnostic imaging method and can be used as an adjunct to coronary interventions. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for intravascular ultrasound as an adjunct for interventional coronary procedures.

Background

Intravascular ultrasound

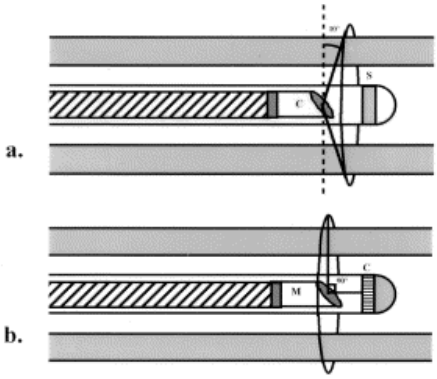
The Procedure

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 with ultrasound. It can be used to determine the extent and composition of atherosclerotic lesions in coronary and peripheral vessels and can measure the burden of non-occlusive atherosclerosis prior to clinical events. In addition to its role in diagnosis and determination of the extent of vessel occlusion, IVUS has evolved into an adjunct to interventional cardiology, particularly in assessment of the appropriate placement of intracoronary stents.

The equipment required to perform intravascular ultrasound consists of two major components: a catheter incorporating a transducer; and a console containing the necessary electrical and computer components to reconstruct the image (Nissen & Yock 2001).

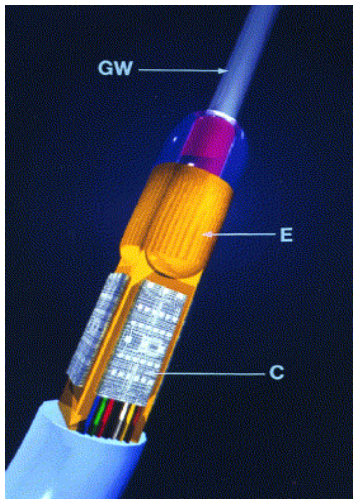
There are two basic transducer technologies to produce catheter based intravascular ultrasound images. One technique employs a mechanical method to generate the ultrasound image, by either rotating the transducer itself (a), or an acoustic mirror (b) (Figure 1). The second method is based on electronic phased array technology, with electronic scanning performed using an array of multiple transducer elements (Figure 2) (Liu & Goldberg 1999; Nissen & Yock 2001).

Figure 1 **Diagrammatic representation of IVUS catheters**



Reproduced from Liu et al (1999) C= transducer crystal, S= septum, M= rotating mirror

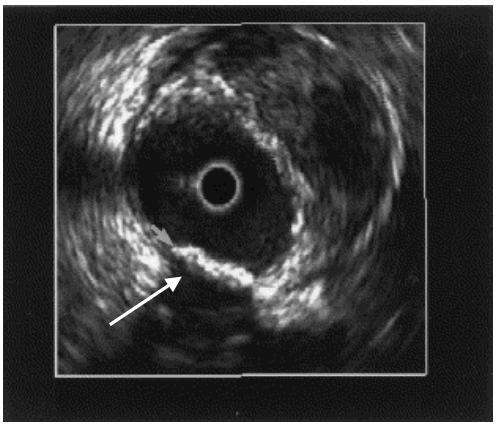
Figure 2 **Electronic phased array catheter based transducer**



Reproduced from Liu et al (1999) E= elements, C = computer chips, GW = central guide wire

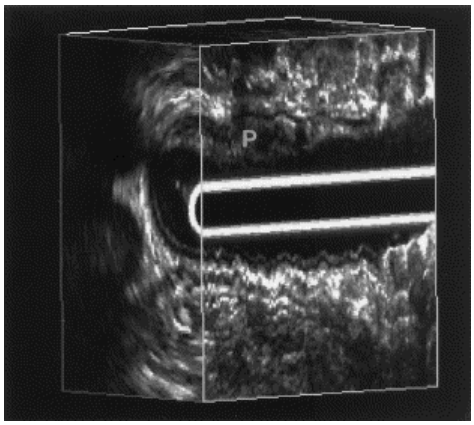
Intravascular ultrasound images the vessel from inside and can provide images of both the lumen and the vessel wall. Using the transducers described above, IVUS can depict cross-sectional luminal size and the shape and thickness of the vessel walls. It can also identify the various layers of the wall in which the intima, media, adventitia and perivascular structures are visible (Liu & Goldberg 1999). It allows the *in vivo* visualisation and quantification of atheroma including the cross-sectional area, and the extent, depth and composition of the plaque, based on acoustic properties of fibrous, lipid and calcified tissue (Liu & Goldberg 1999). This can be done in two dimensions, as cross-sectional or longitudinal images, or sequential images can be reconstructed to provide a three-dimensional (3D) visualisation of a segment of a vessel (Figures 3 & 4).

Figure 3 Cross sectional IVUS image



Reproduced from Liu et al (1999). Arrow indicates calcified plaque, with soft plaque from 12-4 o'clock.

Figure 4 3D IVUS image (Longitudinal view)



Reproduced from Liu et al (1999). Hyperechoic region at (P) atherosclerotic plaque.

Clinical need / burden of disease

Cardiovascular disease comprises all diseases and conditions involving the heart and blood vessels including coronary heart disease, stroke, peripheral vascular disease and heart failure. The main underlying problem in cardiovascular disease is atherosclerosis, the deposition of fat, cholesterol and other substances in the vessels which can lead to occlusion of the blood supply. When atherosclerosis compromises coronary blood supply it can lead to angina, myocardial infarction or sudden death. When the cerebral blood flow is compromised, stroke may result.

Cardiovascular disease is Australia's greatest health problem. It kills more people than any other disease (accounting for 40% of all deaths) and its health and economic burdens exceed that of any other disease. In 1993-94, cardiovascular disease accounted for the largest proportion of health system costs in Australia, $3.7 billion or 12% of total health system costs (Mathers & Penm 1999). Cardiovascular disease accounted for 2% of disease burden in Australia in 1996, 33.1% of premature mortality and 8.8% of years of equivalent 'healthy' life lost through disease, impairment and disability. Coronary heart disease accounts for almost 57% of the cardiovascular disease burden (Mathers, Vos, & Stevenson 1999).

Based on the National Health Survey, an estimated 2.8 million Australians, or 16% of the population, had cardiovascular conditions in 1995. High blood pressure was the most

common condition for both males and females (Australian Institute of Health and Welfare 1999).

Much of the death, disability and illness caused by cardiovascular disease is preventable. Many Australians remain at higher risk of the disease through smoking, being physically inactive, eating a diet high in saturated fats and/or being overweight. Many Australians have blood pressure and/or blood cholesterol above recommended levels; there has been little improvement in physical activity participation, and the proportion of overweight and obese Australians is increasing.

Incidence

Coronary heart disease

There are no national data on the incidence of coronary heart disease in Australia. However, the Universities of Newcastle and Western Australia and the Queensland Department of Health have developed a method to estimate the rate of coronary events among people aged 35-69. Using this method, it is estimated that there were 19,910 coronary events (mainly heart attacks) among people aged 35-69 in 1995-96. Non-fatal heart attacks represented almost two-thirds (12,955 cases) of these events. Non-fatal heart attacks were three times more common among males than females in the 35-69 years age group. Over the period 1984 to 1993, rates of non-fatal heart attacks fell by about 3% per year (Australian Institute of Health and Welfare 1998).

Stroke

Each year, around 40,000 Australians have a stroke, with 70% of these being first-ever strokes. Stroke is the cause of nearly 25% of all chronic disability in Australia (National Health and Medical Research Council 1997). It is more common among older Australians, with around 50% of all strokes occurring in those aged 75 and over. The incidence of stroke is higher in males than in females under the age of 85. For 45 year olds, the risk of having a stroke before age 85 is one in four for males and one in five for females (Australian Institute of Health and Welfare 1999).

Rheumatic fever and rheumatic heart disease

Although this disease is rare among the Australian population overall, its prevalence among Indigenous Australians is one of the highest in the world. The high rates of rheumatic fever among Indigenous peoples are likely to reflect high levels of exposure to group A streptococci, with overcrowding and poor living conditions as major risk factors (Carapetis & Currie 1998).

Mortality

Cardiovascular disease was the leading cause of death among Australians in 1998, accounting for 50,797 deaths or 40% of all deaths. Coronary heart disease was the major cardiovascular cause of death accounting for 55% of all such deaths, followed by stroke (24%), heart failure (5%) and peripheral vascular disease (4%). Cardiovascular mortality is higher among Indigenous Australians, in rural areas of the country, and among socioeconomically disadvantaged groups (Department of Health and Aged Care & Australian Institute of Health and Welfare 1999).

Use of Health services

General practice

A survey of general practice activity found that in 1998-99 cardiovascular problems represented 11% of all problems managed by general practitioners (Britt et al. 1999). Hypertension was the most common cardiovascular problem managed and was the most frequent problem seen in general practice overall, accounting for 5.7% of all problems. Other common cardiovascular problems managed were cardiac check-up (0.9% of problems), coronary heart disease without angina (0.8%) and heart failure (0.6%). Lipid disorder, although not strictly a cardiovascular problem, rated high as well, accounting for 1.7% of problems managed.

Hospitalisation

In 1997-98, cardiovascular disease accounted for 434,748 hospital separations from all public acute and private hospitals in Australia. Of these, 37% were attributed to coronary heart disease, 12% to stroke, 10% to heart failure, 10% to cardiac dysrhythmias, 8% to haemorrhoids, 5% to varicose veins of lower extremities and 3% to peripheral vascular disease (Australian Institute of Health and Welfare 2000a)(see Table 1).

In 1998–99, there were 158,131 hospitalisations where coronary heart disease was the principal diagnosis (3% of all hospitalisations and 36% of hospitalisations for cardiovascular disease). Acute myocardial infarction accounted for 33,908 hospitalisations in 1998–99, 21% of hospitalisations for coronary heart disease.

Table 1 Cardiovascular disease hospital separations (1997-1998)(by sex)

Disease (ICD-9CM code)	Age group (yrs)[a]					
	<15	15-34	35-54	55-74	75+	All ages
Males						
Coronary heart disease (410–414)	0.3	24.3	865.5	4240.0	5615.0	1131.2
Stroke (430–438)	5.6	16.5	101.8	889.2	2981.9	291.3
Peripheral vascular disease (441–444)	0.6	3.7	25.4	351.5	924.6	99.5
Heart failure (428)	2.8	5.0	47.8	596.7	2980.3	226.7
Hypertensive disease (401–405)	4.5	7.0	31.2	84.9	172.4	32.0
Rheumatic fever & rheumatic heart disease (390–398)	3.3	3.2	6.3	22.6	31.8	8.2
All cardiovascular diseases (390–459)	63.3	303.4	1890.8	8562.7	17112.5	2647.3
Females						
Coronary heart disease (410–414)	0.4	7.9	242.4	1840.3	3572.0	586.7
Stroke (430–438)	4.9	16.1	80.1	554.8	2384.7	267.0
Peripheral vascular disease (441–444)	0.1	3.9	14.0	129.6	371.9	49.1
Heart failure (428)	3.3	1.7	23.1	364.4	2452.6	220.8
Hypertensive disease (401–405)	2.8	7.6	36.6	129.6	273.1	50.8
Rheumatic fever & rheumatic heart disease (390–398)	3.9	5.6	10.2	41.7	33.1	14.0
All cardiovascular diseases (390–459)	46.5	288.3	1220.4	4938.3	12517.0	2009.1

[a] Age-specific separations per 100,000 population. (Source: AIHW National Hospital Morbidity Database.)

Cardiovascular procedures

In 1998, there were 17,448 coronary artery bypass graft operations (Australian Institute of Health and Welfare 2000b). Over the same time period there were 18,094 percutaneous transluminal coronary angioplasty (PTCA) procedures performed in Australia. Of these PTCA procedures, 14,838 (82%) patients also had stent placement during the procedure (Table 2).

Table 2 Coronary interventions in 1998

Procedure	ICD-9 CM codes	ICD-10-AM codes	Total Number of procedures[a]	Number of Medicare funded procedures[c]	Cost to Medicare of procedure[e]
Coronary artery bypass	36.1	Block 672 Codes 38497-00 38497-01 38497-02 38497-03 Block 673 Codes 38497-04 Block 674 Codes 38500-00 38503-00	17,448	7,083	$8,883,429
Percutaneous transluminal coronary angioplasty (PTCA)	36.01 36.02 36.05	Block 670 Codes 35304-00 35305-00 (plus Stenting codes below)	18,094	8,916	$3,090,850
Stenting[b]	36.06 36.07	Block 671 Codes 35310-00 35310-01 35310-02	14,838[b]	7,305[d]	$2,838,267[b]
Coronary Angiography	88.55 88.56 88.57	Block 668 Codes 38215-00 38218-00 38218-01 38218-02	77,244	40,721	$15,791,763

[a] Number of procedures for all interventional cardiology units in Australia, based on data from the National Hospital Morbidity Database.

[b] Patients rather than procedures.

[c] These figures include only those services that are performed by a registered provider, for services that qualify for Medicare Benefit and for which a claim has been processed by the HIC. They do not include services provided by hospital doctors to public patients in public hospitals or services that qualify for a benefit under the Department of Veteran's Affairs National Treatment Account (source HIC, 2001).

[d] These form a subset of the PTCA procedures and costs.

[e] Cost to Medicare excluding associated radiological services, preparation, anaesthetics and aftercare (source HIC, 2001).

Existing procedures

Angiography

Angiography is a two dimensional imaging technique which depicts the cross sectional coronary anatomy as a planar silhouette of the contrast filled vessel lumen. Angiography

may be interpreted by readers using direct visual assessment of lesions or by quantitative assessment using computer software.

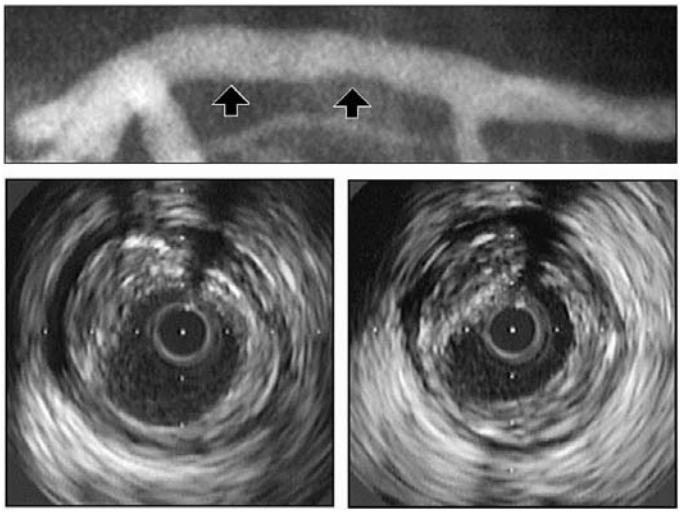
Limitations

Although angiography is the most commonly used method for assessment of coronary artery disease, it has a number of limitations. Visual interpretation of angiograms can result in clinically significant intra- and inter-observer variability (White et al. 1984). In some studies the observer differences in visual estimation of stenosis severity approach 50% (Galbraith, Murphy, & de Soyza 1978; Zir et al. 1976). Studies correlating angiography and post-mortem histopathology have indicated large discrepancies between angiographic severity of lesions and post-mortem histologic examination, with almost all studies demonstrating that angiography underestimates the extent of atherosclerosis and the severity of lesions (Arnett et al. 1979; Grondin et al. 1974; Isner et al. 1981; Vlodaver et al. 1973). In particular, this has been found in patients with 51-75% histopathologic cross sectional area narrowing (Arnett et al. 1979; Hutchins et al. 1977) and in patients with multi-vessel disease (Marcus et al. 1988).

The issue of inter- and intra-observer variability has, in part, been addressed by the development of quantitative coronary angiography, where measurements are at least reproducible (Brown et al. 1986; Goldberg et al. 1990; Reiber et al. 1985). However, despite this, quantitative coronary angiography is still associated with a number of limitations including underestimation of pre-intervention atherosclerosis and inadequate resolution as a result of the complexity of lesions, imaging angles and anatomy of vessels (eg bifurcations, side branches etc).

Extent and severity of stenosis is most commonly assessed by both visual and computer generated measurements of the percentage of stenosis. Percent stenosis is a measure of the luminal diameter within the segment of vessel with lesion compared to that of an adjacent 'normal' section of vessel. An accurate assessment of lesion severity, therefore, is not only dependent upon the true extent of lesion, but also on the 'normal' reference segment of vessel. Necropsy examinations have indicated that atherosclerosis is often diffuse, involving long segments of the diseased vessel. For this reason, a truly normal segment often does not exist for many patients, therefore precluding the accurate calculation of percent diameter reduction or percent stenosis (Nissen & Yock 2001; Ziada et al. 1999). When there is diffuse vessel involvement, the measure of percent diameter stenosis will underestimate the true disease severity (Roberts & Jones 1979; Topol & Nissen 1995; Waller et al. 1992). When there is diffuse, concentric and symmetric disease affecting the length of the vessel, angiography will depict a smaller, but near normal segment (Topol & Nissen 1995).

Figure 5 **Angiographic underestimation of disease. Although angiogram (top) shows only minor luminal irregularities, 2 sites in left anterior descending artery (arrows) show major atherosclerosis by ultrasound (below) (Nissen & Yock 2001).**



Interventions such as angioplasty can increase the complexity and irregularity of the shape of the vessel lumen (Ziada et al. 1999). This means that the lumen silhouette produced by angiography may not be accurate. Necropsy evaluation of post-mechanical intervention vessels indicate that interventions will often lead to fracture or dissection of the plaque which exaggerates lumen eccentricity (Hodgson et al. 1993; Tobis et al. 1989; Topol & Nissen 1995; Waller 1989). As a result of extensive plaque fracture, the angiographic appearance of a dissected post-intervention vessel appears to be an enlarged and often 'hazy' lumen. The enlarged post-procedure lumen therefore often overestimates the vessel cross sectional area and exaggerates the gain in lumen size resulting from the intervention (Topol & Nissen 1995).

Accurate angiographic assessment of the extent and severity of coronary atherosclerosis is also confounded by arterial remodelling (Gruberg et al. 1999; Nissen & Yock 2001; Ziada et al. 1999). Arterial remodelling consists of compensatory dilatation of the external vessel wall in areas with atherosclerotic plaque. In early disease, this vessel enlargement prevents the plaque from encroaching on the vessel lumen, thereby giving the appearance of a normal vessel on angiography. Pathologic studies have indicated that an absolute reduction in the lumen dimensions often does not occur until the lesion occupies approximately 40-50% of the area within the internal elastic membrane (ie 40-50% cross-sectional narrowing) (Glagov et al. 1987; Gruberg et al. 1999; Ziada et al. 1999). As a result of arterial remodelling, angiography will not detect plaque burden less than 40-50% of the total vessel cross sectional area and most of the atherosclerotic burden in a vessel is contained within the angiographically normal reference segments. Although such lesions do not restrict blood flow, observational studies indicate that these lesions are an important predictor for acute coronary syndromes (Little et al. 1988).

Most lesions leading to acute coronary syndromes, unstable angina, myocardial infarction or sudden cardiac death are only considered moderate or non-significant on angiography (less than 50% diameter stenosis) (Ambrose et al. 1985; Little et al. 1988; Vogel 1988). The acute events result from plaque rupture, which contributes to thrombus formation and subsequent vessel occlusion. The fact that so many events occur in angiographically non-significant lesions suggests that lesion characteristics, and not just simply the degree

of stenosis, play a role in determining risk of rupture, subsequent thrombosis, and therefore the likelihood of a clinical event.

The risk of plaque rupture appears to be a combination of intrinsic factors such as plaque composition and inflammatory processes, and extrinsic factors such as tensile and haemodynamic stress (Zaman et al. 2000). The size and consistency of the atheromatous core of a lesion determine lesion stability; the greater the contribution to total plaque size made by the atheromatous core, the more vulnerable the plaque appeared to be to rupture (Davies et al. 1993; Zaman et al. 2000). The structure and strength of the collagen rich fibrous cap are also important determinants of plaque stability, as is the activity of the monocyte/macrophage dependent inflammatory process following plaque disruption (Zaman et al. 2000).

Angiography is a two-dimensional (2D) assessment of lumen dimensions based on contrast filled vessels, with no information on the composition and structure of atherosclerotic lesions.

IVUS is likely to be able to overcome a number of the limitations associated with existing technology, particularly angiography, as described above.

Issues in the evaluation of IVUS

Intended purpose

IVUS can be used as a diagnostic imaging modality for assessment of lesions prior to any intervention. In this setting, IVUS provides additional, complementary information to that already provided by angiography. IVUS may also be used during procedures to monitor and guide catheter based coronary interventions such as balloon angioplasty, stenting and atherectomy.

Principles of diagnostic test evaluation

Evaluation of diagnostic tests

Several authors have discussed the sequence of evaluations that can be done on a diagnostic test (Fukuyama et al. 1994; Jaeschke, Guyatt, & Sackett 1994; National Health and Medical Research Council 2000). These include diagnostic test performance, therapeutic impact and outcome.

Diagnostic test performance ('accuracy') can be measured as sensitivity, specificity, or likelihood ratios. This involves comparing test results against a valid reference or 'gold' standard which represents the 'truth'. Appropriate gold standards can include pathology findings (eg histopathological confirmation of the presence or absence of disease) or clinical outcome (eg subsequent disease progression or resolution of symptoms and signs).

Therapeutic impact is measured as the change in treatment decision made by clinicians in response to the information provided by the test.

Outcome: Do the people who had the test have better health outcomes? This can be assessed by randomised trials of the test and subsequent management resulting from test information. As this is often not available, changes in outcome may be reasonably inferred from a combination of evidence of improved diagnostic accuracy, evidence of changes in management and evidence of the effective treatment of a given condition. That is, in conjunction with evidence of improved diagnostic accuracy and changes in management, there should be evidence (ideally from randomised controlled trials) that alternative treatments or managements result in improved long-term health outcomes for patients. For example if a diagnostic test allowed earlier diagnosis of a condition, evidence that earlier treatment is more effective than delayed treatment is needed to infer that improved outcomes result from the diagnostic test result.

Methodological constraints may prevent some of these studies being done. For example, if it is not possible to measure a reference standard, tests of diagnostic test performance characteristics are not feasible. Assessing diagnostic accuracy will be most relevant when randomised controlled trials suggest that intervention based on that diagnosis is effective.

The following considerations should be given when evaluating diagnostic tests.

Study quality

Studies vary in quality, whether they are looking at diagnostic accuracy or effect on outcomes. Quality influences the reliability and validity of the results of the study. Several checklists of study quality criteria are available, including the NHMRC handbook on how to conduct systematic reviews (National Health and Medical Research Council 2000). Jaeschke et al (1994) indicate that to evaluate whether the results reported in an article about diagnostic tests are valid the issues shown in Table 3 should be considered.

There is potential for verification or 'work-up' bias if the results of IVUS influenced the decision to perform the reference standard (Mielke et al. 1994; Vallabhajosula & Buchsbaum 1994).

Table 3 Evaluating and applying the results of studies of diagnostic tests

Question	Quality indicator
Are the results of the study valid?	
– primary guides	Was there an independent, blind comparison with a reference standard?
	Did the patient sample include an appropriate spectrum of patients to whom the diagnostic test will be applied in clinical practice?
– secondary guides	Did the results of the test being evaluated influence the decision to perform the reference standard?
	Were the methods for performing the test described in sufficient detail to permit replication?
What were the results?	Are the likelihood ratios for the test results presented or data necessary for their calculation provided?
Will the results help me in caring for my patients?	Will the reproducibility of the test result and its interpretation be satisfactory in my setting?
	Are the results applicable to my patient?
	Will the results change my management?
	Will patients be better off as a result of the test?

Source: From Jaeschke et al (1994)

Incremental or replacement test?

In clinical practice IVUS is intended to be used as an incremental test on top of conventional assessment (eg angiography etc), rather than as a replacement test. If IVUS was being evaluated as a replacement test for angiography, then it would be appropriate that the results of the two tests were evaluated blinded and independent from each other to minimise test-review bias. As IVUS will be used in conjunction with angiography and provides complementary information, blinded evaluation of IVUS compared to angiography is not such an issue, as this reflects the way IVUS will be used in clinical practice. If IVUS is viewed as a potential replacement for functional assessments, then the results should be evaluated blind and independent to the comparator.

As IVUS is viewed purely as an additional test on top of conventional assessments, it will have an incremental cost associated with its use, even when used in the diagnostic setting. In this situation, cost offsets could only result from interventions avoided on the basis of IVUS results.

If IVUS is viewed as a potential replacement for some of the functional assessments, then there may also be cost offsets from avoiding these other diagnostic tests, in addition to any changes in management that result from IVUS.

Specific issues for consideration in the evaluation of IVUS as a diagnostic tool

Diagnostic accuracy and reference standard

IVUS provides additional complementary information to that provided by conventional angiography. It should be viewed as an adjunct to angiography rather than as a replacement.

The limitations of angiography have been discussed previously. As a result of these limitations, angiography is not considered an appropriate reference standard for the assessment of the diagnostic accuracy of IVUS.

If the extent of lesions predicts clinical outcome of patients (eg larger lesions are more likely to result in an acute coronary event such as myocardial infarction (MI) or cardiac death) then simply measuring the accuracy of IVUS against histopathological assessment of lesion extent (% diameter stenosis) is appropriate (Ellis et al. 1988). However, as discussed previously, there is evidence to suggest that size of stenosis is only one factor which may influence likelihood of coronary events, as some studies report that 80% of all infarctions occur in lesions with an angiographic diameter stenosis <50% (Little et al. 1988; Vogel 1988). Lesion composition and structure also appear to influence the likelihood of plaque rupture and therefore subsequent thrombosis and clinical events. Given this, it may be more appropriate to measure the accuracy of IVUS against a reference standard of plaque rupture or clinical follow-up for cardiac events.

If lesion composition determines likelihood of rupture, then it may also be possible to measure the diagnostic ability of IVUS to detect those lesions where the composition or structure of the lesion indicates a high likelihood of rupture (ie the composition of a lesion may act as a surrogate measure for actual plaque rupture, thrombosis and clinical events).

Zamen et al (2000) have summarised the characteristics of lesions that affect the risk of plaque rupture (Table 4). They suggest that risk of rupture is influenced by both the plaque's intrinsic vulnerability to rupture and the mechanical stresses acting on the lesion. Intrinsic factors are a reflection of the pathological features and the active disease processes of a lesion, while mechanical stresses result from external physical, haemodynamic and pathophysiological forces which act on the lesion and the vessel wall (Zaman et al. 2000).

Table 4 Factors determining coronary atherosclerotic plaque vulnerability to rupture

Intrinsic factors
Composition
The size and consistency of the lipid core (atheromatous core occupying >40% of total plaque area considered at particularly high risk of rupture and thrombosis)
The structure and strength of the collagen-rich fibrous cap
The active monocyte/macrophage dependent inflammatory processes
Extrinsic factors
Circumferential tensile stress (moderate stenosis > tension than severe stenosis)
Compressive stress (vasoconstriction)
Circumferential bending
Longitudinal flexion stress
Haemodynamic stress (laminar vs oscillatory)

There is some evidence to suggest that the composition of plaque in carotid vessels also affects patient symptomatology and risk of event. Using a measure of Grey Scale Median (GSM) measure, the echogenicity of plaques (Low GSM = hypoechoic = lipid rich) has been examined and correlated with type of symptoms and risk of embolus. It has been found that lesions with low echogenicity are more likely to be symptomatic, while lesions with high echogenicity are more likely to be asymptomatic. It has also been suggested that low echogenicity is associated with embologenicity of lesions (Sabetai et al. 2000; Tegos et al. 2000a; Tegos et al. 2000b; Tegos et al. 2001).

IVUS has a role in detecting these intrinsic factors, particularly those related to plaque composition, prior to clinical symptoms, thereby possibly indicating the lesions at a high risk of subsequent rupture and clinical event. If IVUS is being used in this manner, then an appropriate reference standard may be plaque rupture or a clinical event.

If IVUS is being used to assess the functional severity of atherosclerotic lesions, then it is also possible that it could be assessed relative to a reference standard of functional imaging.

Change in management

Ideally, to assess changes in management patients should have angiography with treatment plans documented as a result of angiography information. IVUS should be done, then treatment plans documented after IVUS. Changes from angiography based plans to IVUS based plans could then be evaluated.

Comparator

IVUS is designed to provide complementary information to that obtained by coronary angiography. In a clinical sense, therefore, there is no real comparator to IVUS.

In terms of this review, the comparator will depend upon the use of IVUS.

In the discussion of diagnostic accuracy of IVUS, angiography is no longer considered the reference standard of coronary imaging due to limitations in resolution, underestimation of extent of disease burden etc, as discussed above. In this setting, IVUS may be compared against a number of reference standards depending on it's purpose. In the case of simple delineation of extent of disease or plaque composition, IVUS can be compared to a reference standard of histopathology (post-mortem specimens or *ex vivo* imaging and histopathology). In the case where IVUS is being used to predict clinical outcome, the appropriate reference standard may be plaque rupture or clinical events.

In the situation where IVUS is used as an adjunct to a coronary intervention, the appropriate comparator is the intervention performed without IVUS guidance (with or without another imaging modality).

Marketing status of the device / technology

The IVUS catheters are listed with the Australian Therapeutic Goods Administration, with the Listing number of AUST L 57575.

Current reimbursement arrangement

Intravascular ultrasound does not currently hold a Medicare Benefit Schedule (MBS) item number for either diagnostic use, or as an adjunct to coronary intervention

Approach to assessment

In undertaking this assessment, the literature available on intravascular ultrasound and its comparators was reviewed, and a supporting committee was convened to evaluate the evidence surrounding the procedure and provide expert advice.

Existing reviews of evidence

A comprehensive health technology assessment of intravascular ultrasound was conducted by the UK National Coordinating Centre for Health Technology Assessment (NCCHTA)(Berry et al. 2000). The focus of this UK assessment was primarily the role of IVUS in the guidance of coronary procedures with the following specific objectives:

> 'To identify literature on IVUS for guiding coronary interventions, and to synthesis 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.'

Research questions

While the assessment of the role of IVUS in the UK was focused mainly on its use as an adjuvant to coronary interventions, the Supporting Committee felt that the more likely role for IVUS in an Australian setting was as a diagnostic imaging procedure. IVUS may be used to determine adequate stent deployment, however, the predominant use in Australia was likely to be to determine whether a lesion was present, the extent of the lesion, and whether an intervention may be required. In this proposed role, an intervention may not occur in a proportion of cases.

Therefore, the research questions specifically addressed relate to:

- the diagnostic accuracy of IVUS; and
- the role of IVUS as an adjunct to coronary interventions (predominantly stenting).

Review of literature

MSAC's recommendations are primarily based on the findings of a systematic literature review conducted by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre (CTC). Papers were also identified from the MSAC application, the NCCHTA report (Berry et al. 2000) and by members of the MSAC Intravascular Ultrasound Supporting Committee (see Appendix B), which was convened to evaluate the evidence and provide expert advice.

The medical literature was searched to identify relevant studies and reviews. As the NCCHTA assessment (Berry et al. 2000) included literature up to the end of 1998, searches for the role of IVUS as an adjunct to coronary interventions spanned the years 1999-2000. Preliminary searches were conducted in August 2000, and final searches were updated in May 2001, to allow for delays in the updating of indexing of studies, particularly in Medline. In addition, information on randomised controlled trials of IVUS was sought from the Supporting Committee members.

As the NCCHTA review did not evaluate the diagnostic accuracy of IVUS as a separate question, the searches for this indication were conducted from 1990 to August 2001.

The following databases were searched to identify literature for inclusion in the review.

- Medline
- National Library of Medicine Health Services Research Databases
  - HealthSTAR
  - HSRProj
  - HSTAT
  - HSR Tools
  - DIRLINE
- CINAHL
- Australasian Medical Index (AMI)
- EBM Reviews – Best Evidence
- Current Contents
- EMBASE
- The Cochrane Library
- ISTAHC Online database (International Society for Technology Assessment in Health Care)
- NHS Centre for Reviews and Dissemination databases
  - DARE (Database of Abstracts and Reviews of Effectiveness)
  - EED (Economic Evaluation Database)
  - HTA (Health Technology Assessment Database)

Search Strategy

Search strategies used to identify IVUS papers in Medline, Current Contents and EMBASE are presented in full in Appendix C.

A broad search using the terms 'IVUS' or 'ICUS' or 'intravascular ultrasound' or 'intracoronary ultrasound' was used for the NHS databases.

Electronic searching also included the Internet sites of the following health technology assessment groups and information sources (Table 5).

Table 5 Health Technology Assessment Organisations

Organisation	Website
International Society for Technology Assessment in Health Care (ISTAHC)	www.istahc.org
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.edu.ca/bcohta
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (US)	www.ohppr.state.or.us/ohrc
Minnesota Department of Health (US)	www.health.state.mn.us
ECRI (US)	www.ecri.org
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veteran's Affairs Research and Development Technology Assessment Program (US)	www.va.gov/resdev
National Library of Medicine Health Service/Technology Assessment text (US)	http://text.nlm.nih.gov
NHS Health Technology Assessment (UK)	www.hta.nhsweb.nhs.uk
Office of Health Technology Assessment Archive (US)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca
Conseil d'Evaluation des Technologies de la Sante du Quebec (Canada)	www.cets.gouv.qc.ca
National Information Centre of Health Services Research and Health Care Technology (US)	www.nlm.nih.gov/nichsr/nichsr.html
Finnish Office for Health Technology Assessment (FinOHTA) (Finland)	www.stakes.fi/finohta/linkit/
Institute Medical Technology Assessment (Netherlands)	www.bmg.eur.nl/imta/
Agencia de Evaluación de Tecnologias Sanitarias (AETS) (Spain)	www.isciii.es/unidad/aet/cdoc.htm
Agence Nationale d'Accreditation et d'Evaluation en Sante (France)	www.anaes.fr

The evidence presented in the selected studies was assessed and classified according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence which is shown in Table 6.

Table 6 Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and more single arm studies or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Source: NHMRC 2000

Search Results

Diagnostic applications of IVUS

The results of applying the search strategies to the main electronic bibliographic databases are shown in Table 7. Due to overlap between databases, a proportion of retrieved citations are duplicated in multiple databases. Table 8 below indicates the number and proportion of citations that remained from each database after exclusion of duplicates.

Table 7 Number of articles retrieved from each database (diagnostic applications)

	Medline	Current Contents	EMBASE	Total
Total # citations	273	12	163	448

Table 8 Number of articles remaining after exclusion of duplicate citations (diagnostic applications)*

	Medline	Current Contents	EMBASE	Total
Total # citations	273	12	163	448
# duplicate citations	4	2	117	123
# citations retrieved not duplicates	269	10	46	325
% of retrieved not duplicates	99%	83%	28%	73%

* This does not take into account multiple publications based on the same data where the citations are different

Therapeutic Applications of IVUS

The results of applying the search strategies to the main electronic bibliographic databases are shown in Table 9. Due to overlap between databases, a proportion of retrieved citations are duplicated in multiple databases. Table 10 below indicates the number and proportion of citations that remained from each database after exclusion of duplicates.

Table 9 Number of articles retrieved from each database (therapeutic applications)(limited to 1999-2000)

	Medline	Current Contents	EMBASE	Total*
Total # citations	715*	404	275	1394
Angioplasty	384	370	175	929
Atherectomy	41	90	38	169
Stenting	324	178	149	651
CABG	209	20	30	259

* Citation numbers do not add to total as citations may have more than one indication

Table 10 Number of articles remaining after exclusion of duplicate citations (therapeutic applications)*

	Medline	Current Contents	EMBASE	Total
Total # citations	715	404	275	1394
# duplicate citations	2	162	171	335
# citations retrieved not duplicates	713	242	104	1059
% of retrieved not duplicates	99.7%	60%	38%	76%

* This does not take into account multiple publications based on the same data where the citations are different

Eligibility criteria for studies

Diagnostic applications of IVUS

There were 325 non-duplicate references identified. The inclusion criteria below were applied to these non-duplicate references:

- $\geq$ 10 patients
- IVUS was compared to an appropriate reference standard (not angiography)
  - histopathological confirmation of extent of disease
  - measures of functional severity of lesions (eg fractional flow reserve, stress myocardial SPECT)
  - clinical outcomes of patients
- Papers which used IVUS as the reference standard for evaluation of other techniques were excluded as they provided no information on the diagnostic accuracy of IVUS per se.

A total of 20 papers met these inclusion criteria. The Supporting Committee provided one additional abstract containing Australian data (Mottram et al. 2000).

Therapeutic Applications of IVUS

As the Berry et al (2000) report provided a comprehensive assessment of the use of IVUS as an adjunct to coronary interventions, a decision was made to update the information provided in their review, specifically with respect to randomised controlled trials published since the end of the date range specified in their searches (end of 1998).

A total of 1,059 non-duplicate citations were identified from the major databases listed above. The following inclusion criteria were applied to these non-duplicate citations:

- Patients undergoing coronary interventions (PTCA, Stenting, atherectomy or CABG)
- Randomised controlled trials of IVUS versus non-IVUS guided interventions

The NCCHTA report (Berry et al. 2000) was identified as the only Level I information available.

Five randomised controlled trials of IVUS guided interventions compared to non-IVUS guided interventions were identified from the literature searches and via Supporting Committee members. One trial (Schiele et al. 1998) was included in the report by Berry et al (2000), and one trial was available only in abstract form at this stage (Russo 1999). These trials were included here, as a meta-analysis of all randomised trials was to be conducted to summarise the results.

- AVID (Russo 1999)
- CRUISE (Fitzgerald et al. 2000)
- SIPS (Frey et al. 2000)
- RESIST (Schiele et al. 1998)
- OPTICUS (Mudra et al. 2001)

Expert advice

A supporting committee with expertise in interventional cardiology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the supporting committee is provided at Appendix B.

Results of assessment

Is it safe?

The safety of intravascular ultrasound has been documented based on clinical surveys and registry data (Batkoff & Linker 1996; Hausmann et al. 1995). This data suggests that complication rates vary between approximately one and three percent, with the most common complication being transient vasospasm. Vasopspasm responds quickly to intravenous nitrates, and some studies indicate that prophylactic nitrate therapy may be given. The rate of major acute procedural complications associated with (but not necessarily caused by) IVUS, such as dissection or vessel closure, is approximately <0.5% (Nissen & Yock 2001). Major complications are more likely to occur in patients undergoing IVUS as part of a therapeutic procedure (eg angioplasty) rather than in a purely diagnostic setting (Nissen & Yock 2001; Tardif 2000). Long-term safety information on IVUS is mainly based on prospective one-year safety data from serial quantitative angiography in cardiac transplant recipients (Pinto et al. 1993). This study found that IVUS did not accelerate the progression of angiographically quantifiable disease, and that it also appeared to be safe for the evaluation of patients not undergoing interventional procedures.

The data available to assess the safety of IVUS is primarily retrospective. For this reason, Quinn et al (2000) have suggested the need for prospective studies to assess the safety of IVUS, in particular the long-term effects of the technique.

Is it effective?

IVUS as a diagnostic tool

Potential role of IVUS

As discussed previously, IVUS is likely to be used in addition to angiography, rather than as a replacement for this imaging, as it provides additional, complementary information. In the assessment of IVUS as a diagnostic imaging modality, it has been assumed that IVUS will be conducted as a pre-intervention assessment of coronary vessels. Of course, IVUS may also be used as a post-intervention diagnostic tool (eg for the assessment of stent placement). However, the post-intervention application of IVUS is covered in the section on the assessment of IVUS as an adjunct to coronary interventions. IVUS could also be used to assess in-stent restenosis (which could be considered post-intervention use), although any papers evaluating this diagnostic application of IVUS will be assessed in this section of the report.

When IVUS is used as a pre-intervention assessment tool it can provide additional information on the likely extent of coronary disease and a better assessment of the normal coronary vessel. It may be useful in the assessment of those patients with apparently angiographically normal vessels who are clinically symptomatic, and in the assessment of angiographically ambiguous or indeterminate lesions, as may occur at bifurcations in vessels. This may influence treatment in a number of ways:

1. By more accurately depicting the true size of the vessel lumen, it may be able to more accurately indicate the most appropriate size of angioplasty balloon or coronary stent.

2. By detecting diffuse disease, it may be possible to avoid inappropriate surgical procedures and alter management to a medical strategy in patients who are a poor surgical risk, or to a more aggressive surgical strategy, eg from PTCA to coronary artery bypass graft (CABG).

3. By better detecting the true extent of disease, appropriate surgical or medical management may be considered in patients where angiographic assessment has indicated normal vessels

4. A proportion of patients present with typical angina and apparently normal coronary angiograms. These patients may have reductions in coronary blood flow resulting from restrictions caused by extraluminal disease. Being a two-dimensional image, angiography will not detect extraluminal disease. IVUS may therefore have a role in the assessment of these patients and be able to provide an informed prognosis and direct appropriate management.

As IVUS is able to determine the composition of atheromatous lesions, and there is some evidence that lipid-rich lesions are at a higher risk of rupture, IVUS may be able to predict which lesions are at a high risk of rupture and therefore which patients may develop subsequent acute coronary syndromes.

Diagnostic accuracy

This section includes discussion of the diagnostic accuracy of IVUS in coronary and peripheral vessels.

Diagnostic accuracy in peripheral vessels

Nishimura et al (1990) evaluated 130 segments of fresh peripheral arteries, and the findings were correlated with corresponding histopathologic sections. It is unclear whether the results of IVUS were assessed independently of the results of the histological examination. The authors indicated that luminal areas determined by ultrasound imaging were highly correlated with those calculated from microscopic slides (r=0.98).

Leertouwer et al (1999) examined the *in vitro* ability of IVUS to characterise renal arteries. Forty-four renal artery specimens (from 21 consecutive humans, recovered at autopsy) were examined with intravascular ultrasound and histopathology. The authors reported that IVUS had a sensitivity of 87% and specificity of 89% for the detection of calcifications. There was insufficient detail in the paper to verify these calculations. Quantitative IVUS analysis was also performed: lumen area, vessel area, plaque area and area obstructed (%) were measured. The authors indicated that intra-observer differences for lumen and vessel area were not significant (p=0.193 and p=0.112).

van Lankeren (1999) investigated the *in vitro* ability of IVUS to detect disruptions of the vessel wall (ruptures and dissections) after balloon angioplasty in 23 plasma perfused post-mortem human iliac arteries with an angiographic stenosis of >30%. Dissections were defined as a radial tear in the internal surface associated with separation of the lesion from the underlying arterial wall; media rupture was an interruption in the internal elastic lamina and media that exposes adventitia to the lumen; and vascular damage was a dissection and/or media rupture. Histopathology was used as the gold standard. IVUS had sensitivities of 77% (95% CI of 63-91%) for detection of any vascular damage, 74% (CI 57-87%) for detection of dissections and 59% (CI 39-78%) for detection of media rupture.

Vogt et al (1998) compared IVUS and angiography to quantify the degree and haemodynamic importance of stenoses in the iliac arteries in 38 patients admitted for angioplasty or femoral bypass surgery. Duplex scanning was used as a reference standard. The authors used a range of cut-off points for IVUS and angiographic measurements to define haemodynamically significant stenoses. Optimal cut-off points for IVUS and angiographic measurements are shown in Table 11.

Table 11 Diagnostic accuracy in the prediction of haemodynamic significance of iliac artery stenoses

Variable	Definition of significant stenosis	Sensitivity	Specificity	Kappa
Angiographic variables				
Percent diameter reduction	>40%	96%	64%	0.64
Percent area reduction	>55%	100%	64%	0.69
IVUS variable				
Percent area reduction	> 55%	96%	86%	0.83

Diagnostic accuracy in coronary vessels

As discussed previously, diagnostic accuracy of IVUS in coronary vessels can be measured from a number of different perspectives, depending upon what IVUS is predicting or measuring.

Extent and type of Lesion

Potkin et al (1990) assessed the *in vitro* reliability of IVUS against a reference standard of histopathology in 21 human coronary arteries from 13 patients with moderate to severe atherosclerosis at necropsy. It is unclear whether IVUS results were assessed blind to histology. The authors report a high level of inter- and intra-observer reliability for both IVUS and histology. Ultrasound and histological measurements correlated highly and significantly ($p<0.0001$) for coronary artery cross-sectional area ($r=0.94$), residual lumen cross-sectional area ($r=0.85$) and percent cross sectional narrowing ($r=0.84$). There was also a high degree of correlation between IVUS and histology in linear wall thickness (plaque and media) ($r=0.92$, $p<0.0001$). Ultrasound also accurately predicted histological plaque composition in 96% of cases.

Bartorelli et al (1990) examined the reliability of IVUS to differentiate plaque morphology subtypes in 60 coronary segments from 33 post-mortem coronary arteries. There is no indication as to whether the IVUS evaluation was performed blind to the reference standard of histopathology. The authors indicated the accuracy of IVUS for detection of fibrous segments was 96%, for lipid rich segments was 78% and for calcification was 100%.

Palmer et al (1999) investigated the *in vitro* ability of IVUS to detect and differentiate atheromatous lesion characteristics in 21 post-mortem human coronary arteries. Two observers were used and a third observer, blind to the IVUS appearances, conducted histopathology as the gold standard. Atheromatous plaque was classified as echodense (hard), echolucent (soft), heterogenous (mixed) or calcified, based on the European Society of Cardiology (ESC) proposed classification of plaque composition (Di Mario et al. 1998). Focal calcification was also detected. Results are displayed in Table 12.

Table 12 Correlation of IVUS images with histology (using proposed ESC classification) - 44 sites

	Sensitivity	Specificity	Positive predictive value	Kappa
Echodense ('hard')	95%	78%	94%	0.93 (0.89-0.97)
Echolucent ('soft')	96%	94%	90%	0.84 (0.79-0.89)
Heterogenous ('mixed')	94%	85%	92%	0.67 (0.63-0.71)
Calcified	92%	100%	91%	0.83 (0.78-0.88)
Overall	94%	89%	92%	0.73 (0.69-0.77)
Focal calcification	96%	99%	91%	0.93 (0.90-0.96)

Scott et al (2000) evaluated the ability of IVUS to detect the extent of calcification of lesions, compared to histopathology. The authors found good correlations between three-dimensional IVUS measurements and histopathology. IVUS-measured calcified luminal surface area (mm^2) correlated highly with pathological assessment ($r=0.82$, $p<0.0001$), as did IVUS-measured percent calcified luminal surface area ($r=0.84$, $p<0.0001$). A more accurate assessment of plaque calcium which incorporates longitudinal extent may affect clinical care and patient outcome. The presence or absence

of calcium has been shown to play a role in interventional success, therefore successful pre-procedure quantification may be helpful.

Prediction of plaque rupture or dissections

Peters et al (1996) investigated the *in vitro* ability of IVUS to detect disruptions of the vessel wall (ruptures and dissections) after balloon angioplasty in 23 plasma perfused post-mortem human coronary arteries with an angiographic stenosis of ≥50%. Ruptures were defined as disruptions of the vessel wall in a radial direction and dissections were defined as disruptions in a circumferential direction. Histopathology was used as the reference standard. Results are shown in Table 13.

Table 13 IVUS detection of plaque dissections and rupture

	Sensitivity	Specificity	PPV	NPV	Accuracy
IVUS prediction of plaque dissection	92%	100%	100%	92%	96%
IVUS prediction of plaque rupture	71%	83%	92%	50%	74%

PPV – positive predictive value; NPV – negative predictive value

van der Lugt et al (1995) investigated the *in vitro* ability of IVUS to detect disruptions of the vessel wall (ruptures and dissections) after balloon angioplasty in 40 post-mortem or explant human coronary arteries with an IVUS measured stenosis of ≥40%. Histopathology was used as the gold standard. The authors found that IVUS had a sensitivity of 79% for detection of dissections, of 76% for the detection of media rupture, but only 37% for the detection of plaque rupture.

van der Lugt et al (1997) firstly conducted an *in vitro* study on 42 atherosclerotic arteries (33 coronary, 9 iliofemoral) where IVUS was compared to histology. Ultrasound images and histologic sections were analysed by two independent and blind observers. The *in vitro* findings were then compared with *in vivo* ultrasound findings in a separate group of 73 patients undergoing balloon angioplasty of the iliofemoral artery. The value of this is unclear, as a different patient group was used for *in vitro* and *in vivo* assessment, and there is no reference standard against which to validate *in vivo* IVUS assessments. Nevertheless, the authors indicated that in the *in vitro* assessment, histology indicated 37 dissections in 42 specimens (88%). IVUS indicated 22 dissections, giving a sensitivity of 59%. Insufficient data was provided to calculate specificity or accuracy. The *in vivo* assessment indicated that IVUS detected dissections at the target site in 46 of 73 patients (63%). It is unclear whether these are pre- or post-intervention IVUS measurements, as both were done. In all cases, the majority of dissection (>80%) were located in the thinnest site of the lesion.

Detection of Thrombus

Franzen et al (1998) examined the ability of IVUS and angiography to detect thrombus formation in coronary stenoses in 20 patients, undergoing 26 procedures. A reference standard of angioscopy was used. Table 14 summarises the diagnostic accuracy of IVUS and coronary angiography for the detection of thrombus.

Table 14 Diagnostic accuracy in the detection of thrombus in coronary stenoses

Variable	Sensitivity	Specificity	PPV	NPV	Accuracy
IVUS	36%	100%	100%	68%	73%
Angiography	36%	87%	67%	65%	65%

PPV – positive predictive value; NPV – negative predictive value

Prediction of functional significance of lesion

Nishioka et al (1999) assessed IVUS measurements for differentiating functionally significant from non-significant coronary stenosis in 70 *de novo* coronary lesions. A reference standard of stress myocardial SPECT imaging was used, and a comparison of standard angiographic measurements was performed. Results are tabulated below (Table 15).

Table 15 Diagnostic accuracy in the prediction of functional severity of coronary stenoses

Variable	Definition of significant stenosis	Sensitivity	Specificity
Angiographic variables			
Percent diameter stenosis	$\geq$ 75%	49%	90%
Percent diameter stenosis	$\geq$ 50%	96%	52%
IVUS variables			
Lesion lumen area	$\leq$ 4 mm^2	88%	90%
Lesion % area stenosis	$\geq$ 73%	84%	81%
Luminal % area stenosis	$\geq$ 59%	86%	81%
Corrected % area stenosis	$\geq$ 75%	86%	81%

Based on these results, the authors suggest that angiography is inappropriate to use, as the standard cut-offs measured by semi-quantitative angiography do not accurately differentiate significant from non-significant lesions. All IVUS measurements have sensitivities and specificities above 80%. Lesion lumen area of $\leq 4mm^2$ is the simplest measure, and provides the highest sensitivity and specificity.

Takagi et al (1999) assessed IVUS measurements for differentiating functionally significant from non-significant coronary stenosis in 70 *de novo* coronary lesions. A reference standard of fractional flow reserve (FFR) was used, with a cut-off of <0.75 indicating significant lesions. The authors determined the parameters where there was best agreement with a fractional flow reserve (FFR<0.75 = functionally significant lesions; FFR $\geq$0.75 not functionally significant). Results are shown in Table 16.

Table 16 Diagnostic accuracy in the prediction of functional severity of coronary stenoses

Variable	Definition of significant stenosis	Sensitivity	Specificity	PPV	NPV	Accuracy
IVUS variables						
IVUS Area stenosis	> 60	92%	88.5%			
Mean Lumen area (mm^2)	< $3mm^2$	83%	92.3%			
IVUS area stenosis > 60 & Mean lumen area <$3mm^2$	Both	88%	100%	100%	90%	94%

PPV – positive predictive value; NPV – negative predictive value

Briguori et al (2001), using a similar methodology to Takagi et al (1999) above, evaluated IVUS measurements for the differentiation of functionally significant from non-significant coronary lesions. Fifty-three *de novo* lesions of intermediate severity (40% to 70% diameter stenosis) from 43 consecutive patients scheduled for routine coronary angiography were evaluated. A reference standard of fractional flow reserve (FFR) was used, with a cut-off of <0.75 indicating significant lesions (FFR <0.75 = functionally significant lesions; FFR $\geq$0.75 not functionally significant). By using receiver operator characteristic (ROC) curves, the values of IVUS measurements (minimal lumen diameter (MLD), minimal lumen area (MLA), lesion length and area percent stenosis) which were most predictive of FFR <0.75 were determined. Results are shown in Table 17.

Table 17 Diagnostic accuracy in the prediction of functional severity of coronary stenoses

Variable	Definition of significant stenosis	Sensitivity	Specificity	PPV	NPV	Accuracy
IVUS variables						
% area stenosis	>70%	100%	68%	69%	100%	87%
MLD (mm)	$\leq$ 1.8mm	100%	66%	46%	100%	79%
MLA (mm^2)	$\leq$ $4mm^2$	92%	56%	46%	96%	79%
Lesion length (mm)	> 10mm	41%	80%	42%	83%	55%
% area stenosis & MLD	>70% & $\leq$ 1.8mm	100%	76%	-	-	-

PPV – positive predictive value; NPV – negative predictive value

Abizaid et al (1998) evaluated the IVUS and angiographic determinants of coronary flow reserve (CFR) as measured by guidewire Doppler velocimetry. A CFR of <2.0 was considered functionally significant. Eighty-six consecutive patients were studied before intervention (n=73) and/or after intervention (n=39, including PTCA and stenting). The authors found that an IVUS minimum lumen cross sectional area (CSA) of $\geq$4.0 mm^2 had a diagnostic accuracy of 89% in identifying a CFR of $\geq$2.0. When only pre-intervention patients were considered, the accuracy improved to 92%. Based on a multivariate analysis, the authors concluded that the major determinants of coronary flow reserve in patients with coronary artery disease were lumen compromise ($p<0.0001$) (measured by IVUS minimum lumen CSA) and lesion length ($p=0.0095$, $r^2 = 0.7176$).

Takayama and Hodgson (2001) evaluated 17 lesions in 15 patients with quantitative coronary angiography (QCA) and 3D IVUS to determine the ability of either technique to predict the physiological significance of coronary lesions. A reference standard of

pressure measurement (FFR and pressure gradient) was used. Three-dimensional IVUS estimated pressure gradients correlated well with actual measured pressure gradients (R^2=0.88, p<0.001). Three-dimensional IVUS estimated FFR also correlated well with the actual FFR measured (R^2=0.90, p<0.001). The authors did not report on the sensitivity and specificity of IVUS and QCA for predicting the functional severity of lesions; rather, they provided the correlation of IVUS and QCA measured parameters with FFR and pressure gradient measurements, as below (Table 18).

Table 18 Correlation of IVUS and QCA parameters with measures of functional severity of lesions (FFR, pressure gradient)

Measure	FFR		Pressure gradient	
	R^2	P value	R^2	P value
QCA measurements				
% diameter stenosis	0.10	0.25	0.20	0.10
Minimum lumen diameter	0.25	0.06	0.17	0.13
Lesion length	0.06	0.40	0.07	0.35
3D IVUS measurements				
Minimum lumen area (MLA)	0.55	0.003	0.52	0.003
% area stenosis	0.55	0.004	0.64	0.004
Lesion length (L)	0.23	0.08	0.45	0.007
MLA / L	0.62	0.005	0.77	<0.001

Prediction of outcome

Ge et al (1999) used IVUS to visualise characteristics of ruptured plaques and correlated these characteristics with clinical symptoms to establish a quantitative index of plaque vulnerability. One hundred and forty-four consecutive patients with angina (age 35-75 yrs) were examined with IVUS, 139 were available for analysis. Ruptured plaques, characterised by a plaque cavity and tear on the thin fibrous cap, were identified in 31 patients (22%) (Group A). Plaque rupture was confirmed by injecting contrast media to fill the plaque cavity during IVUS. Of the patients with plaque rupture, 23 (74%) presented with unstable angina, while in those with no plaque rupture (n=108, Group B) only 19 (18%) had unstable angina. The following parameters were measured in each group: vessel area, plaque area, percent area stenosis, percent diameter stenosis, area of emptied plaque cavity (in ruptured lesions), or echolucent area (in non-ruptured lesions), ratio of echolucent or plaque cavity to plaque area ratio, and thickness of fibrous cap. Results are presented in Table 19 below.

Table 19 Plaque dimensions and characteristics

Characteristic	Mean (SD) and range		p value
	Group A (rupture) n=31	Group B (no rupture) n=108	
Thickness of fibrous cap (mm)	0.47 (0.20) 0.21 – 0.76	0.96 (0.94) 0.4 - 1.7	<0.01
Tear size (mm)	0.83 (0.29)	-	-
Eccentric lesions (%)	94%	64%	<0.01
Plaque size (mm^2)	11.7 (7.0) 4.0 – 30.1	13.4 (8.3) 4.0 – 26.2	NS
Emptied plaque or lipid core size (mm^2)	4.1 (3.2)	1.32 (0.79)	<0.001
Lipid to plaque ratio (%)	38.5 (17.1)	11.2 (8.9)	<0.001
Stenosis (%)	56.2 (16.5)	67.9 (13.4)	<0.001
Superficial calcium deposits	52%	51%	NS
Deep calcium deposits	17%	43%	0.019

NS – not significant

The authors conclude that plaques appear to be at a higher risk of rupture when the echolucent area is larger than 4.1 mm^2 (ie there is a large lipid core), when the echolucent area to plaque ratio (ie. lipid to plaque ratio) is greater than 38.5%, and when the fibrous cap is thinner than 0.7mm. They indicate that this may be useful in determining vulnerable plaques and may influence patient management.

Abizaid et al (1999a) attempted to correlate angiographic and IVUS measures in left main coronary artery (LMCA) disease and to identify the predictors of coronary events at one year in patients with LMCA stenoses. Between November 1991 and December 1997, 355 patients underwent angiographic and IVUS evaluation for LMCA disease. These patients had ischaemic symptoms prior to diagnostic angiography and were referred for IVUS assessment as the angiographic assessment of LMCA lesion severity was inconclusive. Following IVUS evaluation 233 (66%) patients underwent LMCA-related revascularisation procedures, and 122 did not (including 3 where CABG was recommended). These 122 patients were followed for 12 months (1, 3, 6 and 12 months) after the diagnostic imaging. Cardiac events (cardiac death, myocardial infarction and PTCA or CABG related to LMCA) were recorded. Cardiac events in the twelve months included: four cardiac deaths; no MIs; three patients had PTCA of LMCA; and eleven had CABGs. Predictors of cardiac events are tabulated below. A larger number of other clinical, angiographic and IVUS parameters were also tested but were not significant and therefore have not been tabulated.

Table 20 Univariate predictors of coronary events in patients with LMCA disease

	All patients (n=122)	No event (n=104)	Any event (n=18)	p value
Clinical parameters				
Diabetes mellitus n, (%)	32 (26%)	24 (23%)	8 (44%)	0.029
Angiographic findings				
Reference segment (mm)	3.91 ± 0.76	3.98 ± 0.74	3.63 ± 0.81	0.0594
Any treated or untreated vessel (DS >50%)	83 (68%)	69 (66%)	14 (78%)	0.051
Any untreated vessel	39 (32%)	27 (26%)	12 (67%)	0.007
Any treated vessel	63 (52%)	48 (46%)	15 (83%)	0.014
IVUS findings				
Reference segment CSN (%)	37 ± 13	35 ± 12	42 ± 13	0.0418
Lumen CSA (mm^2)	9.3± 5.3	10.0± 5.3	6.8 ± 4.4	0.0127
Maximum lumen diameter (mm)	3.70 ± 0.90	3.85 ± 0.86	3.07 ± 0.77	0.0003
MLD (mm)	2.81 ± 0.82	2.94 ± 0.81	2.30 ± 0.69	0.0012
P&M CSA (mm^2)	12.7 ± 5.9	11.9 ± 5.9	15.7 ± 5.2	0.0077
CSN (%)	57 ± 18	53 ± 18	70 ± 14	0.0002
AS (%)	38 ± 22	34 ± 20	52 ± 21	0.0007

CSN - cross-sectional narrowing; CSA - cross-sectional area; MLD – minimum lumen diameter; P&M – plaque and media; AS – area stenosis; DS – diameter stenosis

Using a multivariate logistic regression analysis, diabetes mellitus, an untreated vessel (with diameter stenosis >50%) and IVUS MLD were independent predictors of cardiac events (Table 21).

Table 21 Multivariate predictors of cardiac events in patients with LMCA disease

	Odds Ratio	95% CI	p value
Diabetes mellitus	6.32	1.82 – 22.04	0.004
Any untreated vessel	3.80	1.08 – 13.39	0.037
IVUS lesion site minimum lumen diameter	0.17	0.05 – 0.59	0.005

The authors concluded that IVUS MLD (mm) was the most important quantitative predictor of cardiac events. For any given MLD, the event rate was exaggerated by the presence of diabetes and another untreated lesion (>50% DS).

Using methodology similar to that described above for patients with LMCA disease Abizaid et al (1999b) also evaluated the use of IVUS in patients without LMCA disease. Between December 1992 and April 1997 IVUS was used to quantify the severity of an intermediate stenosis (<70% diameter stenosis) in 756 patients (900 lesions) without LMCA disease. If stenosis was deemed significant, then an intervention was performed; if not, intervention was deferred. The following patients were excluded from the current analysis: 196 patients who underwent revascularisation procedures as a result of IVUS, and the 260 patients with previously treated lesions. The current analysis was based on 300 consecutive patients with 357 *de novo* intermediate lesions in whom intervention was deferred because of IVUS. Criteria for deferred intervention were generally minimum lumen area $\geq$4mm^2 or MLD $\geq$2 mm. The mean follow-up time was 13 months (1-24 months) and events occurred in 24 patients (8%). Minimum follow-up was 12 months in patients who were event free. There were two cardiac deaths, four patients had MIs and 18 patients had lesion related revascularisation procedures (12 PTCA and 6 CABG).

Diabetes was the only clinical predictor of cardiac events, and all angiographic parameters tested were similar in patients with and without events. Table 22 below indicates those parameters which were significantly associated with cardiac events. As with above, there were other parameters evaluated, however these have not been tabulated as they were found to be non-significant.

Table 22 Univariate predictors of coronary events in patients with *de novo* intermediate coronary stenoses (lesions)

	All patients (n=357 lesions; 300 patients)	No event (n=328 lesions; 276 patients)	Any event (n=29 lesions; 24 patients)	p value
Clinical parameters (patients)				
Diabetes mellitus n, (% patients)	60 (20%)	51 (18%)	9 (38%)	0.017
IVUS findings (lesions)				
Lumen CSA (mm^2)	6.0 ± 2.4	6.2 ± 2.4	4.2 ± 1.2	0.0001
MLD (mm)	2.37 ± 0.49	2.40 ± 0.48	2.00 ± 0.42	0.0001
CSN (%)	57 ± 11	56 ± 12	62 ± 13	0.0288
AS (%)	39 ± 16	37 ± 16	51 ± 15	0.0001

CSN - cross-sectional narrowing; CSA - cross-sectional area; MLD – minimum lumen diameter; AS – area stenosis

Using a multivariate logistic regression analysis, variables tested as possible predictors of cardiac events included diabetes mellitus, IVUS lesion site lumen CSA, MLD, plaque and media CSA, CSN, and AS. Results are shown in Table 23.

Table 23 Multivariate predictors of cardiac events in patients with LMCA disease

	Relative Risk	95% CI	p value
Any Events			
IVUS lumen CSA, (mm2)	0.57	0.400 – 0.842	0.0041
IVUS area stenosis, (%)	1.04	1.006 – 1.082	0.0235
Death / MI			
IVUS MLD (mm)	0.113	0.013 – 0.998	0.0498
Target lesion revascularisation (PTCA or CABG)			
Diabetes mellitus	2.90	1.003 – 8.381	0.0493
IVUS lumen CSA, (mm2)	0.52	0.331 – 0.812	0.0042
IVUS area stenosis, (%)	1.04	0.999 – 1.088	0.0553

CSA - cross-sectional area; MLD – minimum lumen diameter

The authors concluded that in patients with *de novo* intermediate native coronary lesions:

- Coronary angiography could not differentiate lesions with events from those without;
- The event rate was low after IVUS deferred coronary interventions in these patients; and
- The major anatomic predictor of events was IVUS lumen cross-sectional area

Change in management

While not the primary aim of the paper, Abizaid et al (1999a) above, indicated that between November 1991 and December 1997, 355 patients underwent angiographic and IVUS evaluation for LMCA disease. These patients had ischaemic symptoms prior to diagnostic angiography and were referred for IVUS assessment as the angiographic assessment of LMCA lesion severity was inconclusive. Following IVUS evaluation 233 (66%) patients underwent LMCA-related revascularisation procedures, and a further three patients had bypass graft surgery recommended, but refused surgery. The remaining patients had intervention deferred as a result of IVUS.

Abizaid et al (1999b) also evaluated the role of IVUS in patients without LMCA disease, but disease in other vessels. Seven hundred and fifty-six patients (900 lesions) were assessed between December 1992 and April 1997 to quantify the severity of an intermediate stenosis (<70% diameter stenosis). If stenosis was deemed significant an intervention was performed; if not, intervention was deferred. As a result of IVUS, 196 patients (233 lesions) underwent revascularisation procedures (26%).

Mottram et al (2000) report on 16 patients who were referred for CABG following angiographic evidence of LMCA stenosis of indeterminate or intermediate severity. Ten patients had also undergone functional assessments such as stress ECG, stress echocardiography, or thallium imaging. IVUS was performed in all 16 patients. IVUS demonstrated a significant LMCA lesion in seven of 16 patients, while the remaining nine patients were found to have non-significant disease. Of the seven patients with significant disease, five underwent CABG and two were treated medically (one refused surgery, one unsuitable for surgery). Of the nine patients who had non-significant lesions, six were treated medically, and three were treated with PTCA to lesions beyond the LMCA. Currently, this data is available only in abstract form, however, it is understood that a paper has been submitted.

This information suggests that IVUS is able to direct management in patients with indeterminate or ambiguous coronary lesions. In other patient groups, it is reasonable to assume that if IVUS can more accurately determine the extent of lesions, then the treating physician can choose more appropriate therapy. To a certain extent, this aspect of IVUS is also covered below in the discussion of IVUS as an adjunct to coronary interventions.

Change in patient outcomes

Abizaid et al (1999a; 1999b) provide some limited data on cardiac outcomes in patients where IVUS deferred coronary intervention, and these have been discussed above. No data was provided on patients where IVUS information resulted in intervention. There is some data provided in the following section on outcomes of patients with IVUS and non-IVUS guided interventions; however, as yet no comparative data is available on the outcomes of patients where IVUS is used in a purely pre-intervention setting.

Conclusions regarding diagnostic role

IVUS appears to offer additional and complementary information over that provided by coronary angiography. It is able to more accurately demonstrate the likely extent of lesions in both coronary and peripheral vessels. It appears to have good sensitivity and specificity for detection of plaque dissections and media rupture, but lower sensitivity for

the detection of plaque rupture and thrombus formation. It appears to have quite high accuracy in predicting the likely functional severity of lesions. IVUS can also provide information on the composition of plaques. There is some evidence to suggest that selected IVUS parameters may be able to predict clinical events.

There is some evidence that IVUS alters management of patients with angiographically indeterminate or ambiguous lesions. In other patient groups, it may be reasonable to assume that if IVUS can more accurately determine the extent of lesions, then the treating physician can choose more appropriate therapy.

IVUS as an adjunct to coronary interventions

As indicated previously, five randomised controlled trials were identified as comparing IVUS guided interventions with non-IVUS guided interventions:

- AVID (Russo 1999; Russo et al. 2000) [abstracts]
- CRUISE (Fitzgerald et al. 2000)
- SIPS (Frey et al. 2000)
- RESIST (Schiele et al. 1998)
- OPTICUS (Mudra et al. 2001)

A number of endpoints were identified for the evaluation of IVUS as an adjunct to coronary interventions. The end points were ranked as follows:

1. Survival
2. Major adverse cardiac events (MACE)
3. Target lesion/vessel revascularisation (TLR/TVR)
4. Restenosis rate
5. Absolute lumen diameter

Four trials (AVID, CRUISE, OPTICUS and SIPS) addressed both clinical and procedural endpoints; the RESIST trial primarily addressed procedural endpoints.

Each endpoint specified above will be addressed separately.

It was decided *a priori* that the main analyses for these endpoints would not include the AVID trial data, as it is available in abstract form only, and thus, the methodological quality is not able to be assessed. A sensitivity analysis has been conducted for each outcome by including the data from the AVID trial.

It should also be noted that the OPTICUS trial reported the number of events (rather than patients with events) for the outcomes of MACE, myocardial infarction and TLR. It

is also unclear from the paper whether target lesion revascularisation resulted from clinical symptoms (clinically driven TLR) or from imaging detection of significant restenosis that was clinically asymptomatic (angiographically driven TLR). The primary author was contacted in an effort to resolve these issues, however, no response was received. As such it has been assumed that:

- The number of events is the same as the number of patients (ie each patient had only one event); and
- Target lesion revascularisations were driven by clinical symptoms, rather than angiographic evidence of restenosis prior to symptoms.

These assumptions should be borne in mind when interpreting the pooled data presented on the following pages.

Survival

The outcome of survival was addressed by four of the five studies identified (AVID (Russo 1999), CRUISE (Fitzgerald et al. 2000), OPTICUS (Mudra et al. 2001) and SIPS (Frey et al. 2000)). However, it was measured at 12 months for the AVID and OPTICUS trials, at 9 months for the CRUISE trial and at 2 years for the SIPS trial (Table 24). The forest plots below (Figures 6 & 7) have combined outcomes from these different time points, and the limitations of doing this with outcomes measured at different times should be considered when interpreting these results. The RESIST trial (Schiele et al. 1998) did not report survival.

Table 24 Death rates (number and % patients)

Trials	AVID (Russo 1999)		CRUISE (Fitzgerald et al. 2000)		OPTICUS (Mudra et al. 2001)		SIPS (Frey et al. 2000)	
Treatment Arm	IVUS	Non-IVUS	IVUS	Non-IVUS	IVUS	Non-IVUS	IVUS	Non-IVUS
N	394	406	270	229	273	275	121	148
Time point	12 months		9 months		12 months (p=0.121)		2 years	
Death N (%)	12 (3.1)	8 (1.9)	0 (0)	2 (0.9)	5 (1.8)	1 (0.36)	4 (3.2)	4 (2.7)

Figure 6 Forest plot of outcome of death (OR) (without AVID data)

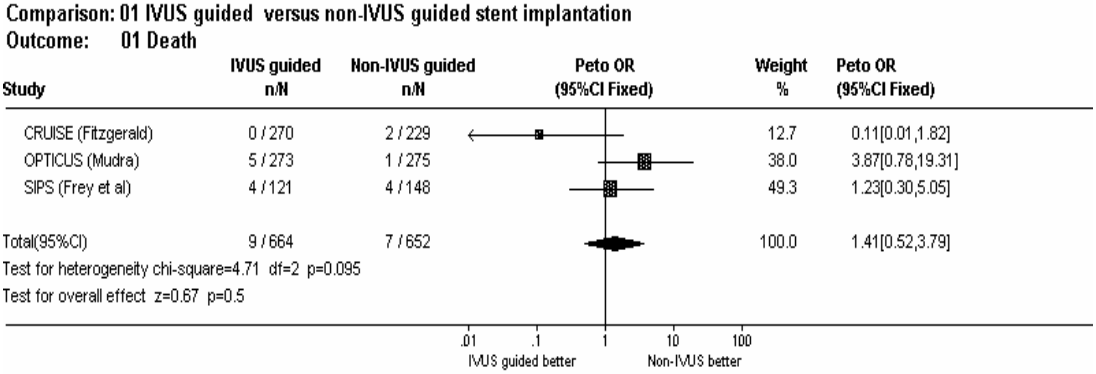
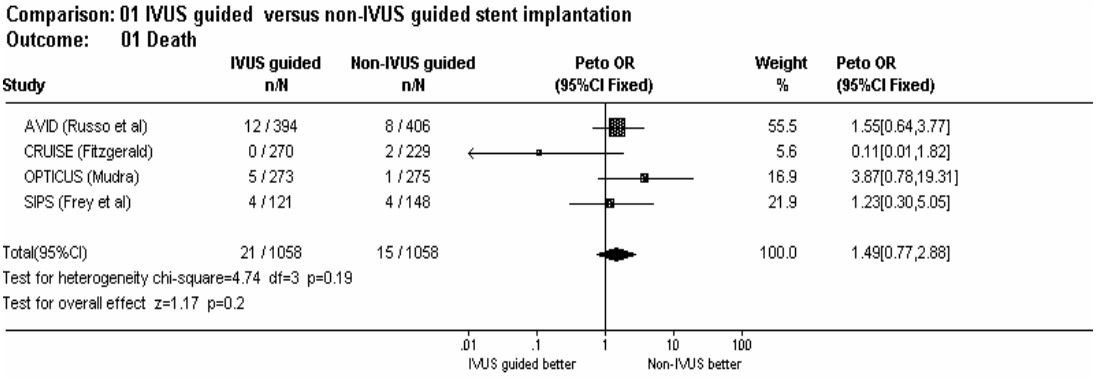


Figure 7 Forest plot of outcome of death (OR) (with AVID data)



As shown above, there was no significant difference in mortality between the treatment groups. The odds ratio of 1.41 (95% CI 0.52 – 3.79) in favour of the non-IVUS guided group was not statistically significant (p=0.5). It can also be seen that the addition of the AVID data made little difference to the overall pooled estimate of effect.

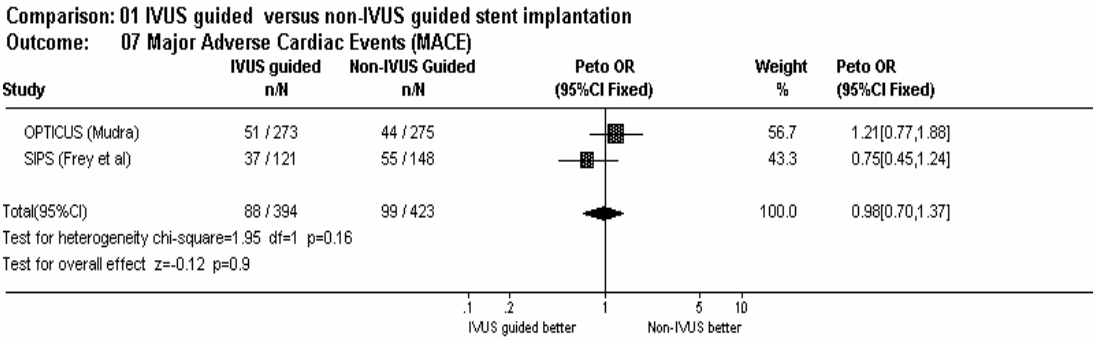
Major Adverse Cardiac Events (MACE)

Only two trials (SIPS and OPTICUS) reported major adverse cardiac events (MACE) as a combined outcome. In this setting, MACE included death, myocardial infarction, re-PTCA and CABG at two years for SIPS and 12 months for OPTICUS (Table 25). OPTICUS data is from a Kaplan-Meier analysis of the proportion of patients without major adverse cardiac events. The forest plot below (Figure 8) has combined outcomes from these different time points, and the limitations of doing this with outcomes measured at different times should be considered when interpreting these results.

Table 25 Major Adverse Cardiac Event (MACE) rates (number and % patients)

Trials	OPTICUS (Mudra et al. 2001)		SIPS (Frey et al. 2000)	
Treatment Arm	IVUS	Non-IVUS	IVUS	Non-IVUS
N	273	275	121	148
Time point	12 months (freedom from MACE)		2 years	
MACE N (%)	51 (18.6)	44 (15.8)	37 (30)	55 (37)

Figure 8 Forest plot for outcome of Major Adverse Cardiac Events (OR)



There was no significant difference in major adverse cardiac events between the treatment groups. The odds ratio of 0.98 (95% CI 0.70 – 1.37) in favour of the IVUS guided group was not statistically significant (p=0.9).

Other trials reported information only on myocardial infarction (as well as separate information concerning deaths and target lesion revascularisation), but did not provide a combined estimate of MACE.

Myocardial Infarction

The outcome of myocardial infarction was addressed by four of the five studies identified (AVID (Russo 1999), CRUISE (Fitzgerald et al. 2000), OPTICUS (Mudra et al. 2001) and SIPS (Frey et al. 2000)). The RESIST trial (Schiele et al. 1998) did not report on myocardial infarction. As with the outcome of mortality, it was measured at 12 months for the AVID and OPTICUS trials, at nine months for the CRUISE trial and at two years for the SIPS trial (Table 26). The forest plots below (Figures 9 & 10) have combined outcomes from these different time points, and the limitations of doing this with outcomes measured at different times should be considered when interpreting these results.

Table 26 Myocardial infarction rates (number and % patients)

Trials	AVID (Russo 1999)		CRUISE (Fitzgerald et al. 2000)		OPTICUS (Mudra et al. 2001)		SIPS (Frey et al. 2000)	
Treatment Arm	IVUS	Non-IVUS	IVUS	Non-IVUS	IVUS	Non-IVUS	IVUS	Non-IVUS
N	394	406	270	229	273	275	121	148
Time point	12 months		9 months (Q-wave MI)		12 months (Q-wave MI)		2 years (Q-wave MI)	
Myocardial Infarction N (%)	26 (6.6)	20 (5.0)	19 (7.0)	14 (6.1)	1 (0.36)	2 (0.73)	1 (0.8)	6 (3.4)

Figure 9 Forest plot for outcome of Myocardial infarction (OR) (Without AVID data)

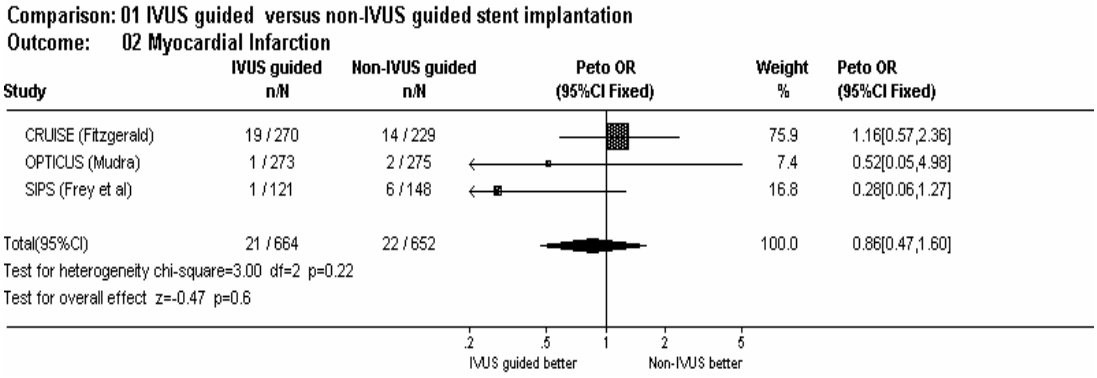
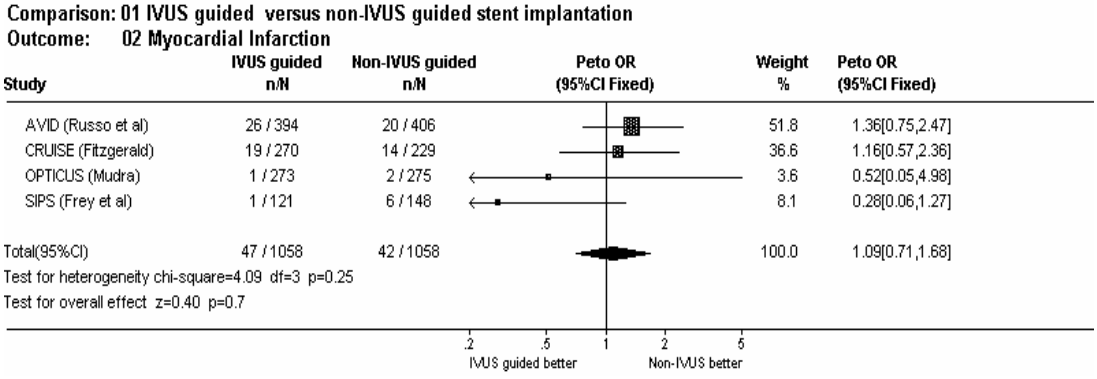


Figure 10 Forest plot for outcome of Myocardial infarction (OR) (With AVID data)



There was no significant difference in the odds of myocardial infarction between the treatment groups. The odds ratio of 0.86 (95% CI 0.47 – 1.60) in favour of the IVUS guided group was not statistically significant (p=0.6). The inclusion of the AVID data changes the direction of the point estimate of the odds ratio (to 1.09, in favour of non-IVUS guided treatment), however the width of the confidence interval (0.71 – 1.68) does not alter the conclusions (p=0.7)

Target Lesion/Vessel Revascularisation (TLR/TVR)

Target lesion revascularisation was defined as any revascularisation procedure such as CABG or repeat PTCA. The outcome of TLR was addressed by four of the five studies identified (AVID (Russo 1999), CRUISE (Fitzgerald et al. 2000), SIPS (Frey et al. 2000) and OPTICUS (Mudra et al. 2001)). The RESIST trial (Frey et al. 2000) did not measure TLR. As with other outcomes, TLR was measured at 12 months for the AVID and OPTICUS trials, at nine months for the CRUISE trial and at two years for the SIPS trial (TVR). It was possible to interpolate nine-month TLR rates (based on number of lesions) for the SIPS trial from the figure below. Using the average number of lesions per patient (1.37 lesions/patient and 1.28 lesions/patient for IVUS and non-IVUS guided groups, respectively) it is possible to estimate the number of patients who underwent TLR at this time point. Data in the table and forest plots (Table 27, Figure 11) are based on these interpolated values.

Figure 11 Figure 1 from SIPS trial (Frey et al. 2000)

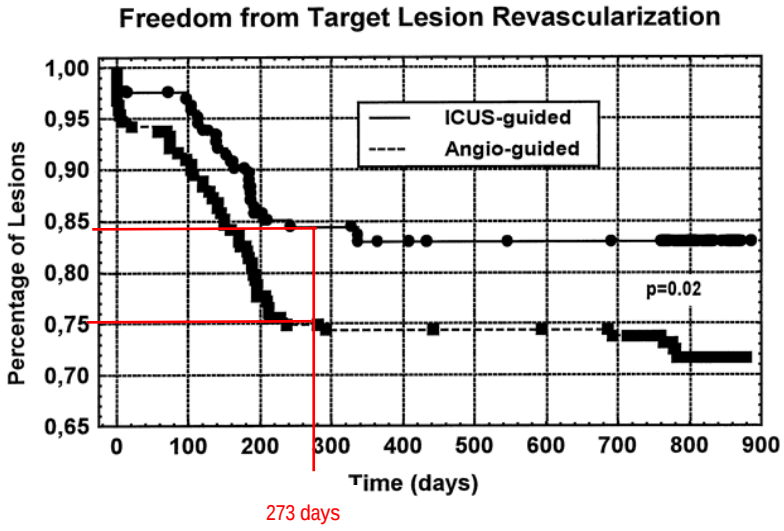


Table 27 Target lesion revascularisation rates (number and % patients)

Trials	AVID (Russo 1999)		CRUISE (Fitzgerald et al. 2000) (clinically driven TLR)		OPTICUS (Mudra et al. 2001)*		SIPS (Frey et al. 2000) (clinically driven TLR)	
Treatment Arm	IVUS	Non-IVUS	IVUS	Non-IVUS	IVUS	Non-IVUS	IVUS	Non-IVUS
N	394	406	270	229	273	275	121	148
Time point	12 months		9 months (TVR)		12 months		9 months	
Target Lesion Revascularisation N (%)	33 (8.4)	50 (12.4)	23 (8.5)	35 (15.3)	41 (15.0)	38 (13.8)	19 (16)	37 (25)

* Please refer to previous comments regarding interpretation of OPTICUS data. N refers to number of events, not number of patients with one or more events, ie a patient could have repeat PTCA and CABG, counted as two events. It is also unclear whether these revascularisation procedures were clinically driven

It is interesting to note that the data from the OPTICUS trial suggests very little difference in the rate of target lesion revascularisation between the IVUS guided and non-IVUS guided arms. The OPTICUS trial was published more recently than the other trials, and it is possible that the patients in the control arm have benefited from changes in balloon expansion (angioplasty) practices over time. It is common now to use oversized angioplasty balloons when deploying stents to attain optimal stent expansion. As a result of these changes, it is possible that the true rate of target lesion revascularisation following stenting in the Australian population may be lower than would be suggested by the control arm rates from the earlier trials.

Figure 12 Forest plot of outcome of target lesion revascularisation (OR) (without AVID data)

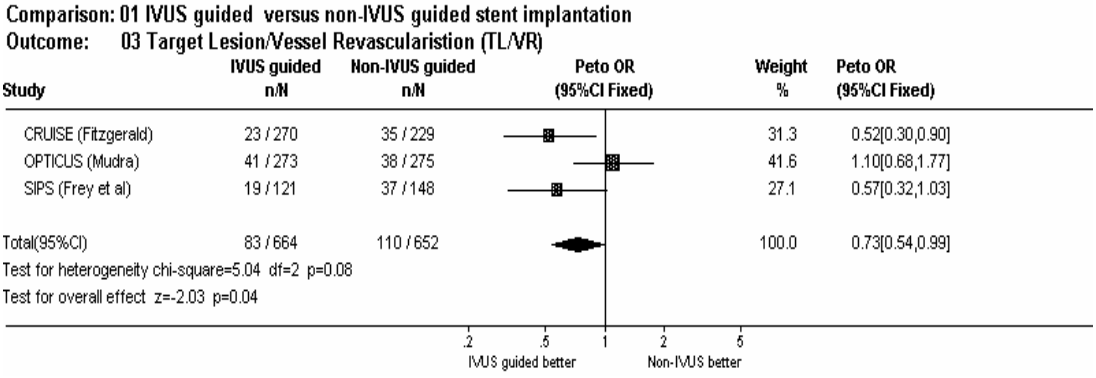
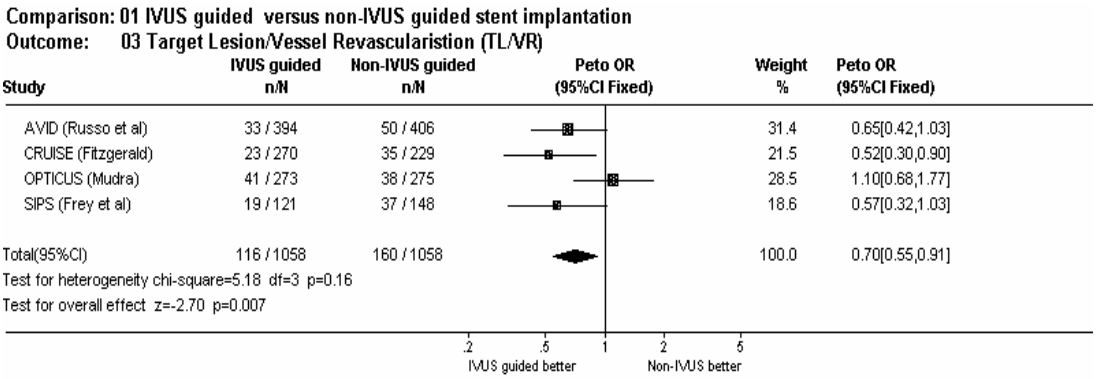


Figure 13 Forest plot of outcome of target lesion revascularisation (OR) (with AVID data)



As can be seen, there was a statistically significant reduction in the odds of patients requiring target lesion revascularisation procedures in the IVUS guided compared to non-IVUS guided treatment groups (OR=0.73, 95% CI 0.54 — 0.99, p=0.04). The addition of AVID data strengthens this conclusion, although there is little change in the estimate (OR=0.70, 95% CI 0.55 — 0.91, p=0.007).

Restenosis rate

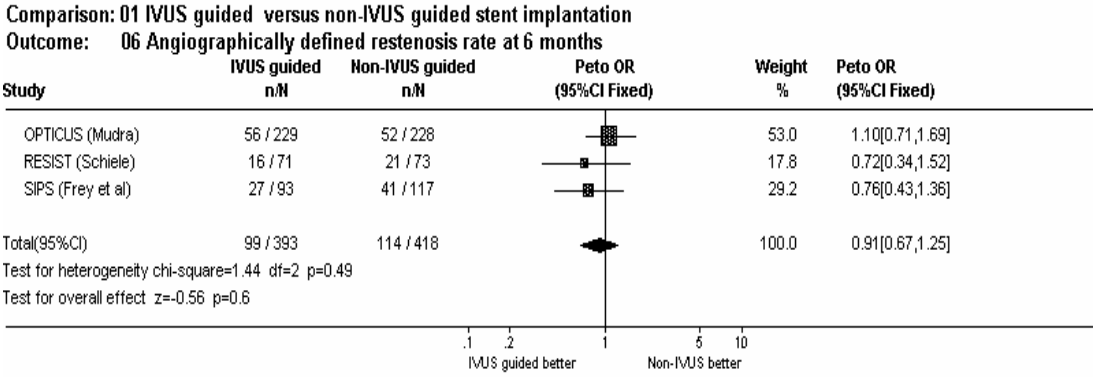
Restenosis rate at six months was also measured by three trials (OPTICUS, RESIST and SIPS). It is unclear how useful this may be as it is measured by angiography, the limitations of which have been discussed previously. The SIPS trial reported restenosis as a percentage of lesions. It was possible to estimate the number of patients this referred to by using the average number of lesions per patient (1.37 lesions/patient and 1.28 lesions/patient for IVUS and non-IVUS guided groups, respectively). The SIPS and OPTICUS trials used a definition of greater than 50% diameter stenosis as a standard measure of restenosis. It is unclear what criteria were used to define restenosis in the RESIST trial. It should also be noted that only a subset of patients from the OPTICUS

trial (84% of the IVUS arm and 83% of the non-IVUS guided arm) underwent follow-up angiography at six months. It is unclear how these patients have been chosen, or whether they are representative of the patients who did not undergo follow-up angiography at six months. Results are shown in Table 28 and Figure 14.

Table 28 Angiographically defined restenosis rate at 6 months (number and % patients)

Trials	OPTICUS (Mudra et al. 2001)		RESIST (Schiele et al. 1998)		SIPS (Frey et al. 2000)	
Treatment Arm	IVUS	Non-IVUS	IVUS	Non-IVUS	IVUS	Non-IVUS
N (patients)	229	228	71	73	93	117
Time point	6 months (p=0.68)		6 month (p=0.25)		6 month (p=0.42)	
Restenosis	56 (24.5)	52 (22.8)	16 (22.5)	21 (28.8)	27 (29)	41 (35)

Figure 14 Angiographically defined restenosis at 6 months (OR)



There was no significant difference in the odds of restenosis at six months between the treatment groups. The odds ratio of 0.91 (95% CI 0.67 – 1.25) in favour of the IVUS guided group was not statistically significant (p=0.6).

Mean Minimal Lumen diameter (MLD)

Absolute lumen diameter was identified as a measure of interest. As no trials reported this exact measure, mean minimal lumen diameter (mm) has been used. Four trials provided information on this outcome; CRUISE (Fitzgerald et al. 2000), OPTICUS (Mudra et al. 2001), RESIST (Schiele et al. 1998) and SIPS (Frey et al. 2000). All four provided information post-procedurally, but only three provided measurements at six months, as tabulated below (Table 29, Figures 15 & 16). It should be noted, however, that only a subset of patients from these trials underwent follow-up angiography at six months. It is unclear how these patients have been chosen, or whether they are representative of the patients who did not undergo follow-up angiography at six months.

Table 29 Mean minimal lumen diameter at post-procedure and 6 months (mm)

Trials	CRUISE (Fitzgerald et al. 2000)		OPTICUS (Mudra et al. 2001)		RESIST (Schiele et al. 1998)		SIPS (Frey et al. 2000)	
Treatment Arm	IVUS	Non-IVUS	IVUS	Non-IVUS	IVUS	Non-IVUS	IVUS	Non-IVUS
MLD (post-procedure)								
N (lesions)[a]	290	253	229	228	79	76	166	190
Mean (SD)	2.9 (0.4)	2.7 (0.5)	3.02 (0.49)	2.91 (0.41)	2.57 (0.41)	2.46 (0.46)	2.49 (0.66)	2.38 (0.67)
MLD (6 months)								
N (lesions)[a]	-	-	229	228	71	73	128	150
Mean (SD)	-	-	1.95 (0.72)	1.91 (0.68)	1.70 (0.64)	1.60 (0.65)	1.71 (0.9)	1.56 (0.9)

[a] N = number of lesions, except for OPTICUS where N = number of patients

Figure 15 Minimal lumen diameter (mm) immediate post-procedural

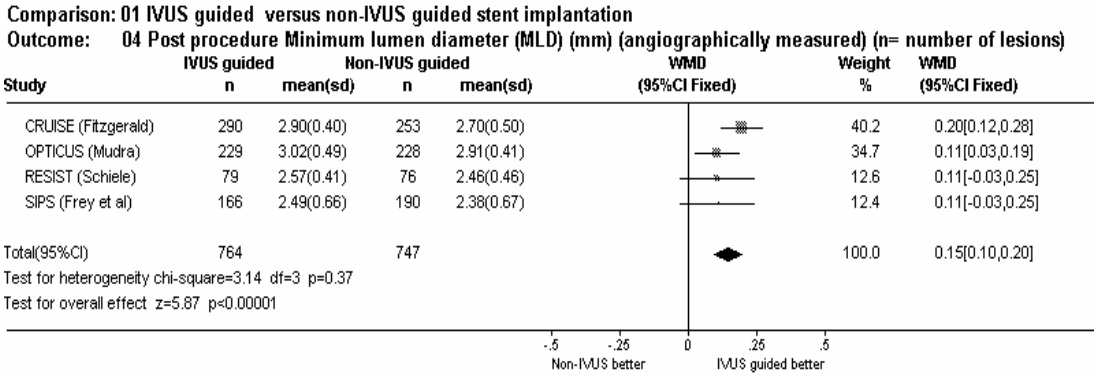
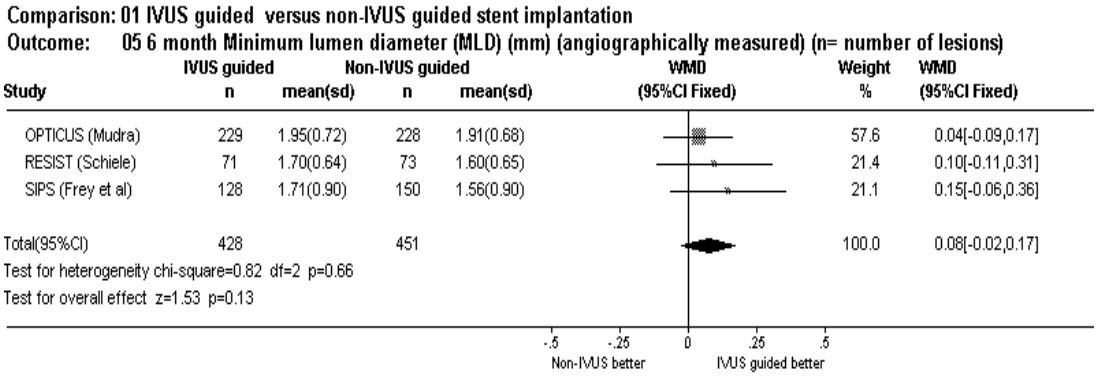


Figure 15 shows that there was a significant improvement in post-procedural angiographically measured mean lumen diameter (mm) for patients treated with IVUS compared to non-IVUS guided interventions ($p<0.00001$).

Figure 16 Minimal lumen diameter (mm) at 6 months



The results in Figure 16 show that there was no significant difference in angiographically measured mean lumen diameter (mm) at six months for patients treated with IVUS compared to non-IVUS guided interventions ($p=0.13$). It is unclear whether this means that the benefit gained post-procedurally does not continue beyond six months, or whether it may be a result of the fact that the largest trial does not present information at this time point, and the analysis is consequently underpowered to detect a difference.

Conclusions

Based on randomised controlled trial evidence, stent placement using IVUS guidance results in a statistically significant reduction in the odds of patients requiring target lesion revascularisation procedures at 9-12 months in the IVUS guided compared to non-IVUS guided treatment groups (OR 0.73, 95% confidence interval 0.54 – 0.99, p=0.04). It should be noted that the upper limit of the 95% confidence interval is approaching the point of no effect (OR = 1). It is unclear at this stage whether the reduction in target lesion revascularisation is sustained over a longer follow-up period. It is also unclear whether it will result in improvements in either Q-wave myocardial infarction or in survival, as the trials were not powered to detect significant differences in either of these parameters.

What are the economic considerations?

The cost effectiveness analysis undertaken is that for IVUS guidance as a routine part of stent placement procedure in interventional cardiology.

Background

A cost effectiveness analysis of IVUS versus non-IVUS guided stent placement has been undertaken previously by the National Health Service in the United Kingdom (Berry et al. 2000). This was done as part of a systematic review with decision analytic modelling of outcomes and cost effectiveness. Based on the systematic review of trial evidence a decision tree was developed for IVUS versus non-IVUS guided stent placement with follow-up conditions, treatments and associated costs.

At the time of the NHS review only one randomised controlled trial (Schiele et al. 1998) and two matched controlled trials (Albiero et al. 1997; Blasini et al. 1998) of IVUS guidance in routine stent placement had been published, each with a primary endpoint of restenosis rate at six months. As a result, the short-term effectiveness of IVUS was measured with a single endpoint of restenosis rate, effectively cropping the decision tree at this point. Reduction in restenosis rate was extrapolated to long-term effectiveness by attributing evidence on long-term quality adjusted life year (QALY) gains from stenting versus PTCA in a previous study by Cohen et al. (1994) to the restenosis reduction from using IVUS relative to non-IVUS guided stenting. Specifically, a derived ratio of 0.24 QALYs gained per restenosis prevented was applied to the reduction in restenosis associated with IVUS guided stenting.

Incremental average utilisation of resources from IVUS versus non-IVUS stent insertion (staff time, disposables) for single vessel disease were identified and were costed using UK prices. Incremental average costs of follow-up conditions and treatment (PCTA and CABG from symptomatic restenosis and MACE) were calculated based on the decision tree and UK prices. Incremental direct costs of treatment and follow-up were then combined to find total average incremental costs.

Current methodology

Estimates of effectiveness

It was decided by the Supporting Committee that clinically driven target lesion/vessel revascularisation (TLR) was a more appropriate clinical endpoint than restenosis rates, as it excluded untreated and asymptomatic restenoses. Three published randomised controlled trials were identified where TLR was an endpoint.

- CRUISE (Fitzgerald et al. 2000)
- OPTICUS (Mudra et al. 2001)
- SIPS (Frey et al. 2000)

Outcome measures from these trials have been discussed in the previous section of this report.

A fourth randomised controlled trial, AVID (Russo 1999; Russo et al. 2000), was identified. However, as the AVID trial is only available in abstract form, it was not used to calculate rates for the model. Comparison of event rates and effects on associated meta-analyses from their inclusion/exclusion are shown in Appendix E.

As the endpoint of TLR was considered more clinically meaningful than restenosis, and was available from randomised controlled trial evidence, a decision tree was proposed that included TLR, MI and death rates as possible clinical endpoints. An *a priori* decision was made to include event types in the decision tree only where randomised evidence on the effects of IVUS was either significant or approaching significance but currently underpowered to detect a likely clinically meaningful difference.

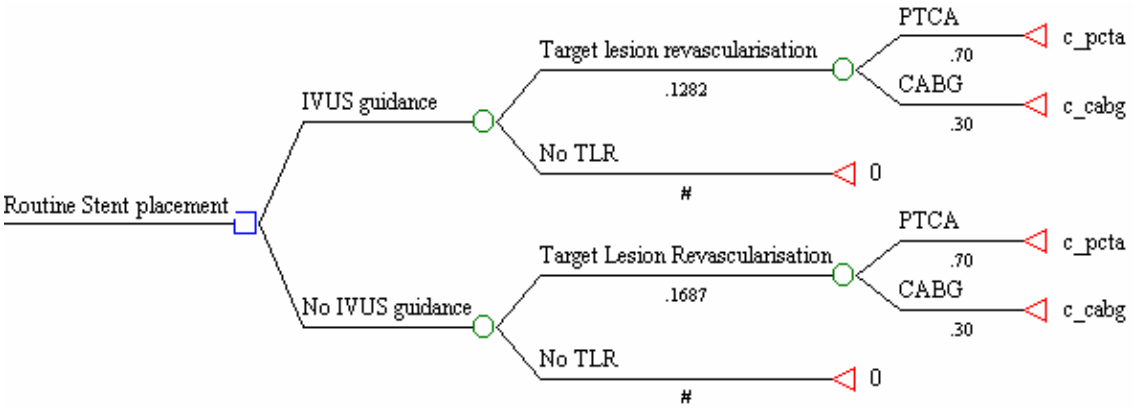
Meta-analyses of the outcomes of TLR, Q-wave MI and mortality from the SIPS, CRUISE and OPTICUS randomised controlled trials were undertaken to calculate relative risks of using IVUS versus non-IVUS guided stent placement. A meta-analysis (using a fixed effects model) of relative risk of target lesion revascularisation using nine month rates of TLR reported in the SIPS (from freedom from target lesion revascularisation curve) and CRUISE trials, and 12 month rates of TLR in OPTICUS was conducted. It found a significant relative risk reduction in TLR of 0.24 (95% CI 0.01 — 0.41) for patients treated with IVUS guided stenting compared to those where IVUS guidance was not used.

TLR rates for IVUS (12.82%) were calculated by applying relative risk of TLR (0.76) with IVUS guided stent placement to combined study base rates reported for TLR, in patients where IVUS guided stent placement was not used (16.87%).

A meta-analysis based on the nine month MI rates from the CRUISE trial, 12 month MI rates from the OPTICUS trial and two year MI rates from SIPS found a relative risk of Q-wave myocardial infarction of 0.86 (95% CI 0.47 — 1.60) for patients treated with IVUS compared to non-IVUS guided stenting. The estimated relative risk reduction was not materially or statistically significant. A meta-analysis based on the nine month mortality rate from the CRUISE trial, 12 month mortality rate from the OPTICUS trial and two year mortality rate for the SIPS trial found a relative risk of mortality of 1.41 (95% CI 0.52 — 3.79) for patients treated with IVUS compared to non-IVUS guided stenting. The estimated relative risk reduction was therefore not statistically significant. Consequently, Q-wave myocardial infarction and mortality rates have not been included in the decision tree or analysis.

The baseline decision tree is indicated below (Figure 17).

Figure 17 Baseline decision analytic model for cost-effectiveness



Estimates of costs

Incremental staffing and disposable costs of undertaking IVUS versus non-IVUS guided stenting have been calculated by applying Australian prices to relative utilisation rates found in the NHS study where appropriate, and including the use of an IVUS catheter (Table 30 & 31). An extra 40% of incremental staff time in procedure was also included as per the method in Berry et al (2000) to allow for staff capital (training, conference time etc).

Table 30 Average incremental cost per patient of extra staff time in performing IVUS guided stent placement

Staff	IVUS guided Units/patient (hrs)	Non-IVUS Units/patient (hrs)	Incremental Units/patient (hrs)	Unit cost ($/hr)	Incremental cost of IVUS per patient
Circulating Nurse	2.01	1.61	0.40	19.47	$7.79
Scrub Nurse	2.01	1.61	0.40	24.12	$9.65
Technician (registrar)	2.01	1.61	0.40	19.42	$7.77
Radiographer	2.01	1.61	0.40	24.31	$9.73
Cardiologist/ Radiologist	2.01	1.61	0.40	82.98	$33.19
Total	2.01	1.61	0.40	-	$68.13

Notes: The extra mean time in laboratory with IVUS is shown by NHS from a study of 19 patients from the Leeds Teaching Hospital NHS Trust to be 24 minutes (124.3 versus 96.3 minutes from table 35,36 of NHS study (2000)). This compares with 15 minutes in the applicants' submission.
Following Berry et al (2000:56), an additional 40% of incremental staff costs to account for staff capital (training) has been included ($27/ procedure).
Extra consumable used per patient in IVUS versus non-IVUS for balloons, guides, sheaths, wires, Iohexol, Lopromide, Sodium Amidotrizoate (Urographin) and Iodixanol are taken from a study of 19 patients form the Leeds Teaching Hospital NHS Trust in Berry et al. (2000). Extra stents per patient are calculated as in NHS study from Albiero et al. (1997), Blasini et al. (1998), Fitzgereald et al. (1999) and the Leeds Teaching Hospital NHS Trust study.

Table 31 Average incremental costs per patient of disposables in performing IVUS guided stent placement

Consumable	IVUS guided Units/patient	Non-IVUS Units/patient	Incremental Units/patient	Unit cost (range)	Incremental cost of IVUS per patient
IVUS catheter	1	0	1	$815	$815
Stents	1.51	1.44	0.07	$1125 (1000-1250)	$78
Balloons	2.53	1.42	1.11	$260 (260-400)	$289
Guide catheter	2.26	1.58	0.68	$75	$51
Sheaths	2.32	2.21	0.11	$14	$2
Wires	2.16	2.37	-0.21	$140	-$29
Iohexol (Omnipaque)	0.26	0	0.26	*	
Iopromide (Isovue)	1.32	1.42	-0.10	*	
Sodium amidotrizoate	1	0.95	0.05	*	
Iodixanol (Visipaque)	0.11	0.05	0.06	*	
Total					$1205

*Drugs have not been costed due to the small effect they have on incremental costs and difficulty in translating to an Australian setting.
Prices other than IVUS catheters are sourced from Royal Prince Alfred hospital cardiac catheter laboratory, who also advised that the use of a single IVUS catheter was additional to guide catheters.
RPA costs: Coronary wires $140; normal balloons $260 but there are specialty balloons used infrequently which cost $400; guides $75 but specialty guides cost up to $140 are also used.
A price of $815 per IVUS catheter was supplied by Boston Scientific as the present average cost of catheters. The cost ranges from $600 in a major teaching hospital in Western Australia to the RPA cost at March 2001 of $950 (note a range of $600-$1000 used in sensitivity analysis).

Based on expert opinion from the Supporting Committee the average capital costs per procedure are calculated for an expected 400 IVUS procedures per machine per year rather than the current 135 procedures to reflect expected practice if approved (Table 32). Capital purchase and maintenance costs of IVUS generators were found by converting costs in the application ($US at time of submission) to $AUD equivalents using exchange rates at the time of analysis.

Table 32 Calculation of average capital costs per procedure

Item	Cost $US (range)	Cost $AUS (range)	Life (range)	Annual cost $AUS /machine (range)
Generator	68,354	132,608	8 (6-10 years)	$16,576 (13261-22101)
Forgone capital return		4% of $132608	Annual	$5304
Maintenance	1000 (500-1500)	1940 (970-2910)	Annual	$1940 (970-2910)
Total opportunity cost of capital				$23820 (19535-30315)
Average cost based on Current procedures/machine/year			135	$176 (144-223)
Average capital cost based on expected procedures per machine per year			400	$60 (48-76)

Notes: The exchange rate used by Boston Scientific at time of submission was US$1 =A$1.58, at time of analysis the exchange rate was US$1=A$1.94. Generator and maintenance costs quoted by Boston Scientific have been taken as US$ equivalents at time of application and converted back to A$ at time of analysis.
Current utilisation rates of 135 procedures per machine annually were seen by the MSAC steering committee to underestimate the expected usage of IVUS as a routine stent placement if approved. An expected rate of 4000 procedures per year has been used to calculate average capital cost per procedure.

Follow-up treatment costs are calculated using average 1997-98 separation weighted Australian version 4.0 diagnosis-related groups (DRG) costs for CABG ($14,297) and PTCA ($4,701) associated with TLR in the decision tree. In the absence of published clinical trial evidence, the proportion of target lesion revascularisations undertaken by CABG was estimated by the supporting committee as 30% (at 9 months follow-up), with sensitivity bounds from 20-40%. The Arterial Revascularization Therapy Study (ARTS) trial reported a 25/75 split in the rate of CABG (3.9%) to PTCA (11.7%) in non-diabetics at one-year follow-up following stent placement. A higher ratio of 36/64 for CABG (8.0%) to PTCA (14.3%) was reported for diabetes patients (Abizaid et al. 2001).

Incremental baseline cost effectiveness is calculated as incremental cost of IVUS divided by incremental reduction in rate of target lesion revascularisation. Target lesion revascularisation is therefore used as the sole (intermediate) endpoint.

Results

Baseline analysis

Baseline results, sensitivity analysis and conclusions are made based on the MSAC decision tree, meta-analyses of TLR and the costs of procedures with follow-up costs of treatment also based on the MSAC decision tree. Meta-analysis of published controlled trials suggests IVUS reduces absolute risk of target lesion revascularisation by 4.05% (relative risk of TLR 0.76 with baseline risk of 16.87%). IVUS results in extra stent placement procedure costs of $1,360, which are offset by incrementally lower average follow-up treatment costs of $307 per patient. This suggests a net average cost increase of $1,053 per patient with IVUS stent placement. The resulting baseline cost per target lesion revascularisation prevented of $26,014 is highly sensitive to the relative risk of target lesion revascularisation (Table 33 and Appendix E, Figure 19).

Table 33 Incremental IVUS guided stent baseline effectiveness, costs and cost effectiveness using Target Lesion Revascularisation as primary endpoint.

Effectiveness and cost per patient	IVUS guided	Non-IVUS guided	Incremental difference
Target lesion revascularisation rate	12.82%	16.87%	- 4.05%
Cost extra staff time- procedure	$68	$0	$68
Cost extra staff time - training etc.	$27	$0	$27
Disposables (excluding drugs)	$3,676	$2,470	$1,205
Capital (including opportunity cost)	$60	$0	$60
Total procedure costs#	$3 831	$2 470	$1 360
Treatment follow-up costs*	$972	$1 279	- $307
Total costs (procedural plus follow-up costs)	$4 801	$3 749	$1 053
Cost effectiveness ($/TLR prevented)			$26 014

procedure costs from Tables 30-32
* follow-up costs based on decision analysis

Sensitivity analyses

The incremental cost/TLR prevented for IVUS guided stent placement was most sensitive to varying the relative risk of target lesion revascularisation through its range (Appendix E, Figure 19). One-way sensitivity analyses indicate lesser but still significant sensitivity to assumptions about the base risk of TLR in the stent implant population considered and a range of costs for the IVUS catheter (Table 34). The addition of the AVID trial data changes the base case incremental cost-effectiveness ratio (ICER) and the upper and lower confidence limits of the relative risk (and therefore ICER), as shown below (Table 35).

Table 34 Sensitivity of incremental cost/ TLR prevented

Sensitivity variable baseline (sensitivity range*)	Cost effectiveness ratio ($/TLR prevented)	
	Lower bound	Upper bound
Cost IVUS catheter $815 ($600,$1000)	$20 703	$30 583
Baseline risk TLR 0.1687* (0.12, 0.22)	$13 185	$39 626
Relative risk TLR 0.76 (0.59, 0.99)*	$12 076	$798 601

* baseline risk based on that of weighted RCT placebo arm risk

Table 35 ICER with AVID data included ($/TLR prevented)

	Cost effectiveness ratio ($/TLR prevented)
Baseline analysis (RR = 0.74)	$27 015
Lower limit of 95% CI (RR = 0.59)	$14 358
Upper limit of 95% CI (RR = 0.92)	$104 827

Limitations of model

Ideally the baseline risk of TLR with stent placement in the Australian population needs to be obtained and compared with that used in this report from controlled trials (16.9%) so that any absolute risk reduction will more accurately reflect local practice.

The randomised controlled trials on which the baseline risk of TLR is calculated were undertaken overseas predominantly prior to 1999. Due to the increase in use of oversized angioplasty balloons during stent placement since this time, the baseline risk of TLR in the current Australian patient population is likely to be lower than is estimated by the randomised controlled trials. Assuming a fixed treatment effect, a baseline risk lower than 16.87% would result in a decrease in the absolute risk reduction with IVUS and increase the cost effectiveness ratio above $26,000 per TLR prevented.

If approved, the true cost of IVUS catheters needs to be established. The average present market price of A$815 reported in correspondence from the applicant and used in this analysis may be reduced (due to economies of scale in production and/or distribution) or increased (due to increased demand) with the wider adoption of IVUS. Present contractual arrangements with hospitals for packages of IVUS catheters linked to purchase price of generators need to be explicitly examined as part of this process.

The intermediate nature of the endpoint of target lesion revascularisation prevented also does not allow easy interpretation or comparison of cost effectiveness. A future study of expected long-term effects on (quality adjusted) survival from reduction in rates of CABG and PTCA outside the scope of this report may therefore also be warranted. To provide an indicative estimate, the approach used by Berry et al (2000) to extrapolate restenosis prevented with IVUS to QALYS saved (using the derived ratio of 0.24 quality adjusted life years saved per restenosis prevented) could be extended to derive a ratio of QALYs saved per TLR prevented. From evidence in Berry et al (2000), approximately 50% of restenoses are symptomatic and lead to TLR. On the assumption that only symptomatic restenosis reduces quality of life, a ratio of double that for restenosis could be inferred for TLR, ie. 0.48 QALYs saved per TLR prevented. This would lead to an indicative estimate of about $54,000 per quality adjusted life year saved from applying the ratio of 0.48 QALYs saved per TLR prevented to the cost effectiveness ratio of $26 014 per TLR prevented. While allowing greater comparison and interpretability of cost effectiveness it should be stressed that an estimate of $54,000 per QALY saved for IVUS guided stenting is indicative only and has significantly greater uncertainty related to it than for cost/TLR prevented derived in the analysis in this report.

An approximate estimate of potential costs of the approval of IVUS guided stenting in Australia is presented in Appendix F.

Conclusions

Using published randomised controlled trial evidence, the baseline cost per clinically-driven target lesion revascularisation prevented from IVUS guided stent deployment is estimated to be $26,000/TLR prevented. A one-way sensitivity analysis, over the 95% confidence interval for relative risk of TLR, estimated a range from $12,000 per TLR prevented to approximately $800,000 per TLR prevented. In general the estimate of cost effectiveness is highly sensitive to estimates of IVUS treatment effect, baseline risk and cost of IVUS catheters.

Conclusions

Safety

Overall, IVUS appears to be a relatively safe procedure. Adverse events appear to relate primarily to vasospasm which can be readily treated with intravenous nitrate therapy. The rate of major acute procedural complications associated with (but not necessarily caused by) IVUS, such as dissection or vessel closure, has been reported to be approximately <0.5%, with major complications more likely to occur in patients undergoing therapeutic IVUS rather than diagnostic IVUS imaging. Long-term safety information based on prospective one-year safety data from serial quantitative angiography in cardiac transplant recipients indicates that IVUS does not accelerate the progression of angiographically quantifiable disease, and that it also appeared to be safe for the evaluation of patients not undergoing interventional procedures.

Effectiveness

Diagnostic applications

IVUS appears to offer additional and complementary information over that provided by coronary angiography. It is able to more accurately demonstrate the likely extent of lesions in both coronary and peripheral vessels. It appears to have good sensitivity and specificity for detection of plaque dissections and media rupture, but lower sensitivity for the detection of plaque rupture and thrombus formation. It appears to have quite high accuracy in predicting the likely functional severity of lesions. IVUS can also provide information on the composition of plaques. There is some evidence to suggest that selected IVUS parameters may be able to predict clinical events.

There is some evidence that IVUS alters management of patients with angiographically indeterminate or ambiguous lesions. In other patient groups, it is reasonable to assume that if IVUS can more accurately determine the extent of lesions, then the treating physician can choose more appropriate therapy.

Therapeutic applications

Based on randomised controlled trial evidence, stent placement using IVUS guidance results in a statistically significant reduction in the odds of patients requiring target lesion revascularisation procedures at 9-12 months in the IVUS guided compared to non-IVUS guided treatment groups (OR 0.73, 95% confidence interval 0.54 – 0.99, p=0.04). It should be noted that the upper limit of the 95% confidence interval is approaching the point of no effect (OR = 1). It is unclear at this stage whether the reduction in target lesion revascularisation is sustained over a longer follow-up period. It is also unclear whether it will result in improvements in either Q-wave myocardial infarction or in survival, as the trials were not powered to detect significant differences in either of these parameters.

Cost-effectiveness

Using published randomised controlled trial evidence, the baseline cost per clinically-driven target lesion revascularisation prevented from IVUS guided stent deployment is estimated to be approximately $26,000 per TLR prevented. This estimate varies from approximately $12,000 to approximately $800,000 per TLR prevented, over the evidence based ranges examined in sensitivity analyses. In general, the estimate of cost effectiveness remains highly sensitive to estimates of IVUS effectiveness.

Recommendation

Since there is currently insufficient evidence pertaining to the effectiveness and cost-effectiveness of intravascular ultrasound as either a diagnostic or therapeutic tool, MSAC recommended that public funding should not be supported at this time for this procedure.

- The Minister for Health and Ageing accepted this recommendation on 17 May 2002 -

Appendix A MSAC terms of reference and membership

The terms of reference of MSAC are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC), and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or Affiliation**
Mr Stephen Blamey (Chair)	general surgery
Professor Bruce Barraclough	general surgery
Professor Syd Bell	pathology
Dr Paul Craft	clinical epidemiology and oncology
Professor Ian Fraser	reproductive medicine
Associate Professor Jane Hall	health economics
Dr Terri Jackson	health economics
Ms Rebecca James	consumer health issues
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Ageing
Associate Professor Richard King	internal medicine
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Mr Lou McCallum	consumer health issues
Emeritus Professor Peter Phelan	paediatrics

Dr Ewa Piejko	general practice
Dr David Robinson	plastic surgery
Professor John Simes	clinical epidemiology and clinical trials
Professor Richard Smallwood	Chief Medical Officer, Commonwealth Department of Health and Ageing
Professor Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council
Associate Professor Ken Thomson	radiology
Dr Douglas Travis	urology
Professor David Weedon	pathology (Chair until 24/08/01)
Ms Hilda Bastian	consumer health issues (Member until 24/08/01)
Dr Ross Blair	vascular surgery (New Zealand) (Member until 24/08/01)
Dr Paul Hemming	general practice (Member until 24/08/01)

Appendix B Supporting committee

Supporting committee for MSAC application 1032 Intravascular ultrasound

Dr John Primrose (Chair from Sept. 2001) MBBS (Hons), FRANZCR Senior Medical Adviser Health Access and Financing Division Commonwealth Department of Health and Ageing	Medical adviser to MSAC
Dr Ross Blair (Chair until August 2001, then a corresponding member) MBChB, RACS Thoracic and Vascular Surgeon Director of Vascular Surgery Waikato Hospital, New Zealand	Member of MSAC until August 2001
Dr Douglas Cavaye MBBS, FRACS Consultant Vascular Surgeon	Nominated by the Royal Australian College of Surgeons
Dr Charles Fisher BSc (Med), MBBS, FRACS, Cert US, MmedClEpi Consultant Vascular Surgeon	Nominated by the Australian Society of Ultrasound in Medicine
Associate Professor David Muller MD, FRACP, FACC Interventional Cardiologist St Vincent's Hospital, Darlinghurst	Nominated by the Cardiac Society of Australia and New Zealand
Associate Professor Kenneth Thomson MbChB, FRACR, AmBdR, FRCR Director of Radiology Alfred Hospital, Prahran	Nominated by the Royal Australian and New Zealand College of Radiology

Appendix C – Search Strategies

The search for IVUS publications was broadly categorised into:

- IVUS as a diagnostic tool; and
- IVUS as an adjunct to coronary interventions.

The search strategies are detailed in Tables 36-40.

Diagnostic applications of IVUS

Table 36 Search Strategy for IVUS as a diagnostic tool (Medline)

	Search Terms	Hits
1	exp Ultrasonography, Interventional/	3131
2	intravascular ultras$.mp.	1606
3	intracoronary ultras$.mp.	282
4	IVUS.mp.	585
5	ICUS.mp.	1159
6	(intensive care unit$ adj4 ICU$).mp.	2975
7	5 not 6	520
8	ICU.mp.	7631
9	7 not 8	284
10	1 or 2 or 3 or 4 or 9	4155
11	(sensit$ or specific$).mp.	1244844
12	10 and 11	690
13	exp Cardiovascular Diseases/	1033935
14	12 and 13	329
15	limit 14 to (human and english language)	273
16	limit 15 to yr=1990-2001	273

Table 37 Search Strategy for IVUS as a diagnostic tool (Current Contents)

	Search Terms	Hits
1	exp Ultrasonography, Interventional/	0
2	intravascular ultras$.mp.	1980
3	intracoronary ultras$.mp.	563
4	IVUS.mp.	519
5	ICUS.mp.	730
6	(intensive care unit$ adj4 ICU$).mp.	2050
7	5 not 6	276
8	ICU.mp.	4089
9	7 not 8	165
10	1 or 2 or 3 or 4 or 9	2271
11	(sensit$ or specific$).mp.	826165
12	10 and 11	253
13	Cardiovasc$.mp.	45339
14	12 and 13	14
15	limit 14 to (english language and yr=1990-2001)	12

Table 38 Search Strategy for IVUS as a diagnostic tool (EMBASE)

	Search Terms	Hits
1	exp Intravascular Ultrasound/	1062
2	intravascular ultras$.mp.	1948
3	intracoronary ultras$.mp.	268
4	IVUS.mp.	623
5	ICUS.mp.	1035
6	(intensive care unit$ adj4 ICU$).mp.	2795
7	5 not 6	451
8	ICU.mp.	6642
9	7 not 8	240
10	1 or 2 or 3 or 4 or 9	2307
11	(sensit$ or specific$).mp.	1005897
12	10 and 11	266
13	exp Cardiovascular Disease/	744434
14	exp Coronary Artery Disease/	39197
15	13 or 14	744434
16	12 and 15	209
17	limit 16 to (human and english language and yr=1990-2001)	163

Therapeutic applications of IVUS

Table 39 Search Strategy for IVUS as an adjunct to coronary interventions (Medline and Current Contents)

	Search Terms	Medline Hits	Current Contents Hits
1	exp Ultrasonography, Interventional/ or exp Ultrasonography/	107935	N/a
2	intravascular ultras$.mp.	1606	1980
3	intracoronary ultras$.mp.	282	563
4	IVUS.mp.	585	519
5	ICUS.mp.	1159	730
6	(intensive care unit$ adj4 ICU$).mp.	2975	2050
7	5 not 6	520	276
8	ICU.mp.	7631	4089
9	7 not 8	284	165
10	1 or 2 or 3 or 4 or 9	108637	2271
11	exp ANGIOPLASTY/ or exp ANGIOPLASTY, BALLOON/ or exp ANGIOPLASTY, BALLOON, LASER-ASSISTED/ or exp ANGIOPLASTY, LASER/ or exp ANGIOPLASTY, TRANSLUMINAL, PERCUTANEOUS CORONARY/ or angioplasty.mp.	27660	16366
12	10 and 11	2088	1171
13	limit 12 to (human and english language and yr=1999-2000)	384	370
14	exp ATHERECTOMY/ or exp ATHERECTOMY, CORONARY/ or atherectomy.mp.	1799	1598
15	10 and 14	260	339
16	limit 15 to (human and english language and yr=1999-2000)	41	90
17	exp STENTS/ or stents.mp.	13118	5220
18	10 and 17	1035	483
19	limit 18 to (human and english language and yr=1999-2000)	324	178
20	exp Coronary Artery Bypass/ or CABG.mp.	24659	2258
21	20 or coronary artery bypass.mp.	27297	7246
22	10 and 21	1273	63
23	limit 22 to (human and english language and yr=1999-2000)	209	20
24	13 or 16 or 19 or 23	715	404

Table 40 Search Strategy for IVUS as an adjunct to coronary interventions (EMBASE)

	Search Terms	Hits
1	exp ULTRASOUND/ or exp INTRAVASCULAR ULTRASOUND/	16541
2	intravascular ultras$.mp.	1947
3	intracoronary ultras$.mp.	268
4	IVUS.mp.	616
5	ICUS.mp.	964
6	(intensive care unit$ adj4 ICUs).mp.	331
7	5 not 6	633
8	ICU.mp.	6078
9	7 not 8	228
10	1 or 2 or 3 or 4 or 9	17594
11	exp ANGIOPLASTY/ or angioplasty.mp. or exp PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY/ or exp TRANSLUMINAL CORONARY ANGIOPLASTY/	21886
12	10 and 11	794
13	limit 12 to yr=1999-2000	175
14	exp ATHERECTOMY/ or atherectomy.mp.	1705
15	10 and 14	220
16	limit 15 to (human and yr=1999-2000)	38
17	exp Coronary Stent/	1783
18	10 and 19	218
19	limit 20 to (human and yr=1999-2000)	149
20	exp Coronary Artery Bypass Graft/ or CABG.mp.	10721
21	22 or coronary artery bypass graft.mp.	11168
22	10 and 23	93
23	limit 24 to (human and yr=1999-2000)	30
24	16 or 18 or 21 or 25	275

Searches of other sources

Organisation	Website/source	Search Terms	Hits
Australian Medical Index (AMI)	Webspirs from Silver Platter	“intravascular ultrasound”	5
International Society for Technology Assessment in Health Care (ISTAHC)	www.istahc.org	"intravascular ultrasound" OR "intravascular ultrasonography" OR "intravascular sonography" OR "IVUS" in title or abstract field	2
NHS Databases (DARE, EED, HTA)	http://144.32.228.3/scripts/WEBC.EXE/nhscrd/restart	"intravascular(w)ultrasound/all fields OR intravascular(w)sonography/all fields OR intravascular(w)ultrasonography/all fields"	7
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org	See above, NHS databases	
HealthSTAR	http://igm.nlm.nih.gov/	"intravascular ultrasound" OR "intravascular ultrasonography" OR "intravascular sonography" OR "IVUS" (Exclude Medline overlap)	60
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.edu.ca/bcohta	“intravascular” or “ultrasound”	0
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se	“intravascular” or “ultrasound”	0
Oregon Health Resources Commission (US)	www.ohppr.state.or.us/ohrc	“intravascular” or “ultrasound”	0
Minnesota Department of Health (US)	www.health.state.mn.us	“intravascular” or “ultrasound”	0
ECRI(US)	www.ecri.org	“intravascular” and “ultrasound”	0
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca	“intravascular” or “ultrasound”	0
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca	“intravascular” or “ultrasound”	0
Veteran’s Affairs Research and Development Technology Assessment Program (US)	www.va.gov/resdev	Intravascular ultrasound	1
National Library of Medicine Health Service/Technology Assessment text (US)	http://text.nlm.nih.gov	"intravascular ultrasound" OR "intravascular ultrasonography" OR "intravascular sonography" OR "IVUS"	0
NHS Health Technology Assessment (UK)	www.hta.nhsweb.nhs.uk		1
Office of Health Technology Assessment Archive (US)	www.wws.princeton.edu/~ota	“intravascular” or “ultrasound”	0
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca	“intravascular” or “ultrasound”	0
Conseil d’Evaluation des Technologies de la Sante du Quebec (Canada)	www.cets.gouv.qc.ca	“intravascular” or “ultrasound”	0
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/nichsr/nichsr.html	“intravascular” or “ultrasound”	0
Finnish Office for Health Technology Assessment (FinOHTA) (Finland)	http://www.stakes.fi/finohta/linkit/	“intravascular” or “ultrasound”	0
Institute Medical Technology Assessment (Netherlands)	http://www.bmg.eur.nl/imta/	“intravascular” or “ultrasound”	0
Agencia de Evaluación de Tecnologias Sanitarias (AETS) (Spain)	http://www.isciii.es/unidad/aet/cdoc.htm	“intravascular” or “ultrasound”	0

Organisation	Website/source	Search Terms	Hits
Agence Nationale d'Accreditation et d'Evaluation en Sante (France)	www.anaes.fr	"intravascular" or "ultrasound"	0
DIMDI- German Institute for Medical Documentation and Information	www.dimdi.de	"intravascular" or "ultrasound"	2
New Zealand Health technology Assessment	http://nzhta.chmeds.ac.nz/	"intravascular" or "ultrasound"	0
Agency for Healthcare Research and Quality	http://www.ahrq.gov/	"intravascular" or "ultrasound"	0

Appendix D Studies included in the review

Table 41 Diagnostic applications of IVUS

Study & Design	Study purpose	Patient Population	Interpretation of IVUS	IVUS results	Any comparator results	Conclusions / comments / limitations	Reference Standard
Peripheral vessels							
(Nishimura, Edwards, & Warnes 1990)	To correlate IVUS luminal areas with histopathology	N = 130 segments of peripheral artery	Unclear whether blinded	Luminal areas determined by IVUS highly correlated with those calculated from microscopic slides (r=0.98)	N/a		Histopathology
(Leertouwer et al. 1999)	*In vitro* ability of IVUS to characterise renal arteries	44 renal artery specimens from 21 consecutive humans	Not reported	Detection of calcification Sn 87% Sp 89%	N/a		Histopathology
(van Lankeren et al. 1999)	*In vitro* ability of IVUS to detect disruptions of vessel wall (ruptures & dissections) after balloon angioplasty	23 plasma perfused human iliac arteries with angiographic stenosis > 30%	Not reported	Detect any vascular damage Sn 77% (CI 63-91) Detect dissections Sn 74% (CI 57-87) Detect media rupture Sn 59% (CI 39-78)			Histopathology
(Vogt et al. 1998)	Quantify the degree and hemodynamic importance of iliac artery stenoses	38 patients admitted for angioplasty or femoral artery bypass surgery	Not reported	Various cut off points for angiog. and IVUS used IVUS % area reduction > 55% Sn 96% Sp 86% Kappa 0.83	Angiography % diameter reduction >40% Sn 96% Sp 64% % area reduction >55% Sn 100% Sp 64%	IVUS better, angiography compromised specificity too much.	
Coronary vessels							
(Potkin et al. 1990)	*In vitro* reliability of IVUS to characterise lesions	21 coronary arteries from 13 patients with mod—severe atherosclerosis	Blind to histology	Correlations with Histo Coronary artery CSA r=0.94, p<0.0001 Residual lumen CSA, r=0.85 % CS narrowing, r=0.84 IVUS accurately predicted histological plaque composition in 96%			Histopathology
(Bartorelli et al. 1990)	Reliability of IVUS to differentiate plaque morphology subtypes	60 coronary segments from 33 post mortem coronary arteries	Not reported	Accuracy for fibrous segments: 96% Accuracy for lipid-rich segments: 78% Accuracy for calcification: 100%			Histopathology

Study & Design	Study purpose	Patient Population	Interpretation of IVUS	IVUS results	Any comparator results	Conclusions / comments / limitations	Reference Standard
(Mottram et al. 2000)	Usefulness of IVUS in patients with indeterminate or intermediate lesions on angiography	N=16 Patients referred for CABG following angiographic evidence of LMCA stenosis	Not stated	IVUS indicated 7 significant LMCA lesions and 9 non-significant lesions. Of 7 significant, 5 had CABG, 2 medical treatment (1 refused CABG, 1 not fit) Of 9 non-significant, 6 medically managed and 3 PTCA instead	N/a	IVUS prevented the inappropriate CABG surgery in nine of 16 patients with indeterminate or intermediate lesions on angiography. Provides information on changes in management, rather than diagnostic accuracy	N/a
(Palmer et al. 1999)	*In vitro* ability of IVUS to detect and differentiate atheromatous lesion characteristics	21 post mortem human coronary arteries	Blind to histopathology	Hard plaques Sn 95% Sp 78% PPV 94% Soft plaques Sn 96% Sp 94% PPV 90% Mixed plaques Sn 94% Sp 85% PPV 82% Calcified plaques Sn 92% Sp 100% PPV 91% Focal calcification Sn 96% Sp 99% PPV 91%			Histopathology
(Scott et al. 2000)	Ability of IVUS to detect the extent of calcifiction of lesions	Not reported	Not reported	IVUS measured calcified surface area highly correlated with pathological assessment (r-0.82, p<0.0001) IVUS measured % calcified luminal surface area highly correlated with pathology (r=0.84, p<0.0001)		More accurate assessment of plaque calcium incorporating longitudinal extent may affect clinical care and patient outcome as presence/absence of calcium shown to play a role in interventional success	Histopathology
(Peters et al. 1996)	*In vitro* ability of IVUS to detect disruptions of vessel wall (dissections and ruptures) after balloon angioplasty	23 plasma perfused post mortem human coronary arteries with angiographic stenosis $\geq$ 50%	Not reported	Plaque dissection Sn 92% Sp 100% PPV 100% NPV 92% Acc 96% Plaque rupture Sn 71% Sp 83% PPV 92% NPV 50% Acc 74%			Histopathology

Study & Design	Study purpose	Patient Population	Interpretation of IVUS	IVUS results	Any comparator results	Conclusions / comments / limitations	Reference Standard
(van der Lugt et al. 1995)	*In vitro* ability of IVUS to detect disruptions of vessel wall (dissections and ruptures) after balloon angioplasty	40 post mortem or explant human coronary arteries with IVUS stenosis ≥ 40%	Not reported	Plaque dissection Sn 79% Media rupture Sn 76% Plaque rupture Sn 37%			Histopathology
(van der Lugt et al. 1997)	*In vitro* ability of IVUS to detect disruptions of vessel wall (dissections and ruptures) after balloon angioplasty	42 atherosclerotic arteries 73 patients undergoing IVUS	Blinded to histology	Authors report that for the *in vitro* assessment, histology detected 37 dissections in 42 specimens, and IVUS detected 22 of these (Sn 59%) *In vivo*, IVUS detected dissection in 46 of 73 patients (63%), unclear how many were true positive etc.		The value of comparing *in vitro* with *in vivo* findings in two separate patient groups is unclear No reference standard available for validation of *in vivo* results	Histopathology (for *in vitro* IVUS)
(Franzen, Sechtem, & Hopp 1998)	To assess the ability of IVUS and angiography to detect thrombus formation	20 patients, undergoing 26 procedures	Not reported	Sn 36% Sp 100% PPV 100% NPV 68% Acc 73%	Angiography Sn 36% Sp 87% PPV 67% NPV 65% Acc 65%		Angioscopy
(Nishioka et al. 1999)	To assess the ability of IVUS and angiography to differentiate functionally significant from non-significant coronary stenoses	70 *de novo* coronary lesions	Not reported	Lesion lumen area ≤ 4mm^2 Sn 88% Sp 90% Lesion % area stenosis ≥ 73% Sn 84% Sp 81% Luminal % area stenosis ≥ 59% Sn 86% Sp 81% Corrected % area stenosis ≥ 75% Sn 86% Sp 81%	Angiography % diameter stenosis ≥ 75% Sn 49% Sp 90% % diameter stenosis ≥ 50% Sn 96% Sp 52%	Authors concluded angiography is inappropriate to use and standard cut offs on angiography do not accurately differentiate significant from non-significant lesions (low values of either Sn or Sp) All IVUS measurements have Sn & Sp > 80%, lesion lumen area is simplest to measure with best accuracy	Stress myocardial SPECT
(Takagi et al. 1999)	To assess the ability of IVUS to differentiate significant from non-significant lesions	70 *de novo* coronary lesions	Not reported	% area stenosis > 60% Sn 92% Sp 88.5% Mean lumen area < 3mm^2 Sn 83% Sp 92.3% Both Sn 88% Sp 100% PPV 100% NPV 90% Acc 94%			Fractional flow reserve (FFR)

Study & Design	Study purpose	Patient Population	Interpretation of IVUS	IVUS results	Any comparator results	Conclusions / comments / limitations	Reference Standard
(Briguori et al. 2001)	To assess the ability of IVUS to differentiate significant from non-significant lesions	53 *de novo* coronary lesions of intermediate severity (40-70% diameter stenosis) from 43 consecutive patients	Not reported	% area stenosis > 70% Sn 100% Sp 68% PPV 69% NPV 100% Acc 87% Mean lumen diameter ≤ 1.8 mm Sn 100% Sp 66% PPV 46% NPV 100% Acc 79% Mean lumen area ≤ 4mm^2 Sn 92% Sp 56% PPV 46% NPV 96% Acc 79% Lesion length > 10 mm Sn 41% Sp 80% PPV 42% NPV 83% Acc 55% % area stenosis > 70% and MLD ≤ 1.8mm Sn 100% Sp 76%		ROC curves used to determine optimal cut points to predict FFR < 0.75	Fractional flow reserve (FFR) FFR < 0.75 = functionally significant lesion
(Abizaid et al. 1998)	Evaluation of IVUS and angiographic determinants of coronary flow reserve (CFR)	86 consecutive patients were studied before (n=73) and/or after (n=39) interventions	Not reported	Authors reported that IVUS minimum lumen CSA of ≥ 4.0 mm^2 had a diagnostic accuracy of 89% in identifying a CFR of ≥ 2.0 When only pre-intervention patients considered, accuracy improved to 92%		Based on multivariate analysis authors concluded major determinants of CFR in patients with CAD were lumen compromise ($p<0.0001$) (lumen CSA) and lesion length ($p=0.0095$, $r^2 = 0.7176$)	Coronary flow reserve (CFR) CFR< 2.0 considered functionally significant
(Takayama & Hodgson 2001)	To evaluate the ability of angiography and 3D IVUS to predict the physiological significance of coronary lesions	17 lesions in 15 patients	Not reported	3D IVUS pressure gradients correlated well with actual measure pressure gradients (R^2=0.88, $p<0.001$), and actual measured FFR (R^2=0.90, $p<0.001$)			Pressure measurement (fractional flow reserve and pressure gradient)

Study & Design	Study purpose	Patient Population	Interpretation of IVUS	IVUS results	Any comparator results	Conclusions / comments / limitations	Reference Standard
(Ge et al. 1999)	IVUS used to visualise characteristics of ruptured plaques and correlated characteristics with clinical symptoms to establish quantitative index of plaque vulnerability	144 consecutive patients with angina examined with IVUS, 139 available for analysis		Thickness of fibrous cap – significantly lower in ruptured plaques ($p<0.01$) % eccentric lesions – sig higher in ruptured plaques ($p<0.01$) emptied plaque or lipid core size (mm^2), sig higher in ruptured plaques ($p<0.001$) lipid to plaque ratio sig higher in ruptured plaques ($p<0.001$) % stenosis, significantly lower in ruptured plaques ($p<0.001$) % deep calcium deposits, significantly lower in ruptured plaques ($p=0.019$)		Authors conclude that plaques appear to be at higher risk of rupture when echolucent area is > 4.1 mm^2, when echolucent area to plaque ratio is > 38.5% and when fibrous cap is < 0.7mm	
(Abizaid et al. 1999a)	Attempt to correlate angiographic and IVUS measurements in LMCA disease and to identify predictors of events at one year in patients with LMCA stenoses	355 patients btwn Nov 1991 and Dec 1997 underwent angiography and IVUS evaluation for LMCA disease Ischaemic symptoms prior to angiography and were referred for IVUS as angiographic assessment of severity was inconclusive.	N/a	233 pts had revascularisation procedures undertaken after IVUS, and 122 did not. These 122 pts followed for 12 months and cardiac events were recorded At 12 months: 4 cardiac deaths, no MIs, 3 had PTCA of LMCA, 11 CABGs Authors performed univariate analysis of clinical, angiographic and IVUS parameters (see publication) In multivariate logistic regression diabetes mellitus (OR 6.32, $p=0.004$), an untreated vessel with >50% diameter stenosis (OR 3.80, $p=0.037$) and IVUS lesion MLD (0.17, $p=0.005$) were independent predictors of cardiac events.		Authors concluded IVUS MLD was most important quantitative predictor of cardiac events. For any given MLD, the event rate was exaggerated by the presence of diabetes and another untreated lesion (> 50% DS)	

Study & Design	Study purpose	Patient Population	Interpretation of IVUS	IVUS results	Any comparator results	Conclusions / comments / limitations	Reference Standard
(Abizaid et al. 1999b)	IVUS used to quantify severity of intermediate stenoses (< 70% diameter stenosis)	756 patients (900 lesions) btwn Dec 1992 and April 1997 If stenosis deemed significant on IVUS then intervention was performed, if not, then intervention was deferred. Following patients excluded: 196 who underwent revascularisation as a result of IVUS, 260 with previously treated lesions		Current analysis based on 300 consecutive patients with 356 *de novo* intermediate lesions for whom intervention was deferred due to IVUS. Mean follow-up 13 months (1-24 mo); events occurred in 24 patients: 2 cardiac deaths, 4 MIs, 18 revascularisations (12 PTCA, 6 CABG) Univariate predictors of events in paper. Multivariate: Any events: IVUS lumen CSA (OR 0.57, p=0.0041), IVUS % area stenosis (OR 1.04, p=0.0235) Death or MI IVUS MLD (OR 0.113 p=0.0498) TLR ({TCA or CABG) diabetes mellitus (OR 2.90, p=0.0493) IVUS lumen CSA (OR 0.52, p=0.0042) IVUS % area stenosis (OR 1.04, p+0.0553)		Authors concluded in patients with *de novo* intermediate native coronary lesions, 1. Angiography could not differentiate lesions with events from those without 2. Event rate was low after IVUS deferred coronary interventions 3. Major anatomic predictor of events was IVUS lumen CSA	

Table 42 Randomised controlled trial assessment of the therapeutic application of IVUS as an adjunct to coronary stenting - trial characteristics

Study	Randomisation	Centres	Allocation concealment	Blinding	Outcome assessment	Follow-up	Methods	Control Group	Treatment Group
AVID (Russo 1999) NB abstract only	Yes Method not stated Dates not reported	24 US centres	Not reported	No	Not reported	1mo 6mo 12mo	After elective coronary stent placement and optimal angiographic result (< 10% residual stenosis by angiography), patients were randomised to angiography or IVUS guided therapy. Blinded IVUS was performed in angiography group with no further therapy; in the IVUS group, IVUS criteria for optimal stent placement)< 10% stenosis, absence of dissection, full stent apposition) were applied	N=406	N=394
CRUISE (Fitzgerald et al. 2000)	Yes, patients randomised as part of The STARS trial Method not stated Centres assigned to perform either IVUS guidance or angiographic guidance April 1996 – May 1997	16 US sites STARS 45 US sites	Not reported	No	Clinical data independent-ly adjudicated	9mo	CRUISE is a sub-study of the STARS trial. 16 centres selected on the basis of experience with IVUS imaging in previous trials. Authors indicate to avoid influencing the primary randomisation in the STARS trial, the use of IVUS was assigned on a centre-by-centre basis (ie each centre performed either IVUS or angiography). In angiography centres, a blinded documentary IVUS examination was performed after stent optimisation (<10% diameter stenosis). In the IVUS group, after angiographic success IVUS performed to optimise stent deployment (could use higher pressure, larger balloons, additional stents etc). Post procedure patients were randomly assigned to one of the STARS regimens (long-term aspirin 325mg alone, long-term aspirin 325mg + ticlopidine 250mg bd, 1 mo; or long-term aspirin 325mg plus adequate coumarin to maintain INR between 2.0 and 2.5 for 4 weeks	525 patients randomised, not stated to which groups	
								N=7 centres N=229 pts at 9 mo follow-up	N=9 centres N=270 pts at 9 mo follow-up

Study	Randomisation	Centres	Allocation concealment	Blinding	Outcome assessment	Follow-up	Methods	Control Group	Treatment Group
OPTICUS (Mudra et al. 2001)	Yes Off site, remote fax from central office October 1996 – February 1998	26 German centres	Yes	No	Angiographic and IVUS parameters measured blind Not reported whether clinical endpoints were meas. blind	1mo 6mo 12mo	Patients were reandomised to ultrasound guided stent implantation or angiography guided stent implantation. A minimal balloon pressure of 14 atm was recommended. In patients assigned to ultrasound guided stenting, pre-interventional ultrasound assessment was recommended. All ultrasound performed with motorised pull back (0.5mm/s) after IC injection of nitroglycerin. In patients with US guidance, MUSIC criteria for optimal stent deployment were used; and for angiography a < 10% residual diameter target was used. Patients were treated with IV heparin to achieve activated clotting time of $\geq$ 300s, and after the procedure, with combined aspirin ($\geq$ 100mg/day) for an indefinite duration and ticlopidine 250mg BID for 4 weeks.	N=277 randomis-ed N=275 treated (269 as random.) ITT analysis	N= 273 randomis-ed N=273 treated (252 as random.) ITT analysis
RESIST (Schiele et al. 1998)	Yes Method not stated January 1995 – February 1997	Multi centre, France Number of centres not reported	Not reported	Single blind	Not reported	6mo	Randomisation was done after stent implantation after angiographic result was judged satisfactory. IVUS imaging performed in all patients, but no further dilatation performed in the control group, whereas additional balloon inflations performed in IVUS group until criterion for stent expansion was reached. Criterion: ratio of intrastent CSA to average proximal and distal reference lumen CSA, with cut off point of 80% Heparin therapy stopped 24 hours after angioplasty, patients continued aspirin 250mg and ticlopidine 500mg for 1 month	N= 76	N= 79

Study	Randomisation	Centres	Allocation concealment	Blinding	Outcome assessment	Follow-up	Methods	Control Group	Treatment Group
SIPS (Frey et al. 2000)	Yes 'consecutive patient randomised design study' 'day to day block schedule'; performed on the morning of each day February 1996 – May 1996	1 German centre	Not reported	No	Not reported	6mo angiog 2 yrs clinical	A total of 491 consecutive patients (595 procedures) treated during study period, only 269 patients included, 203 excluded as had chronic total occlusion (others unclear) A strategy of provisional stenting was used, ie not all patients had stents and stenting was discouraged unless a significant dissection was present after angioplasty, or unless angiographic results were unacceptable. For angiography patients, the operator was encouraged to achieve an optimal result predefined as < 35% residual angiographic diameter stenosis, if stents used, the target criterion for success was < 10% diameter stenosis with no evidence of uncovered dissection. In IVUS patients where stenting used MUSIC criteria used to define successful implantation; in patients with no stents, repeat interventions (ie angioplasty) done with IVUS guidance until the minimal lumen area within the lesion was > 65% of the mean reference area Periprocedural medication included oral aspirin (100mg po) and heparin (10,000-20,000 IU IV) during procedure. Patients who had stents treated with 250-500mg aspirin IV and ticlopidine 250mg bd (unknown duration)	N=148	N=121

Appendix E Economic analysis

Figure 18 Meta-analysis of TLR rate: IVUS vs Non-IVUS guided stenting

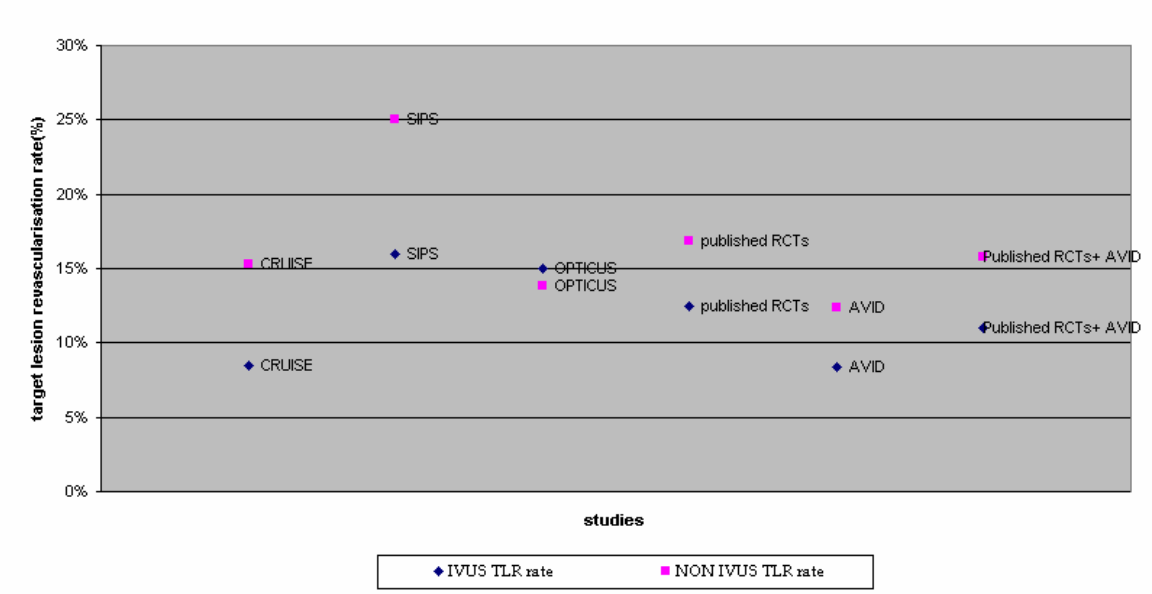
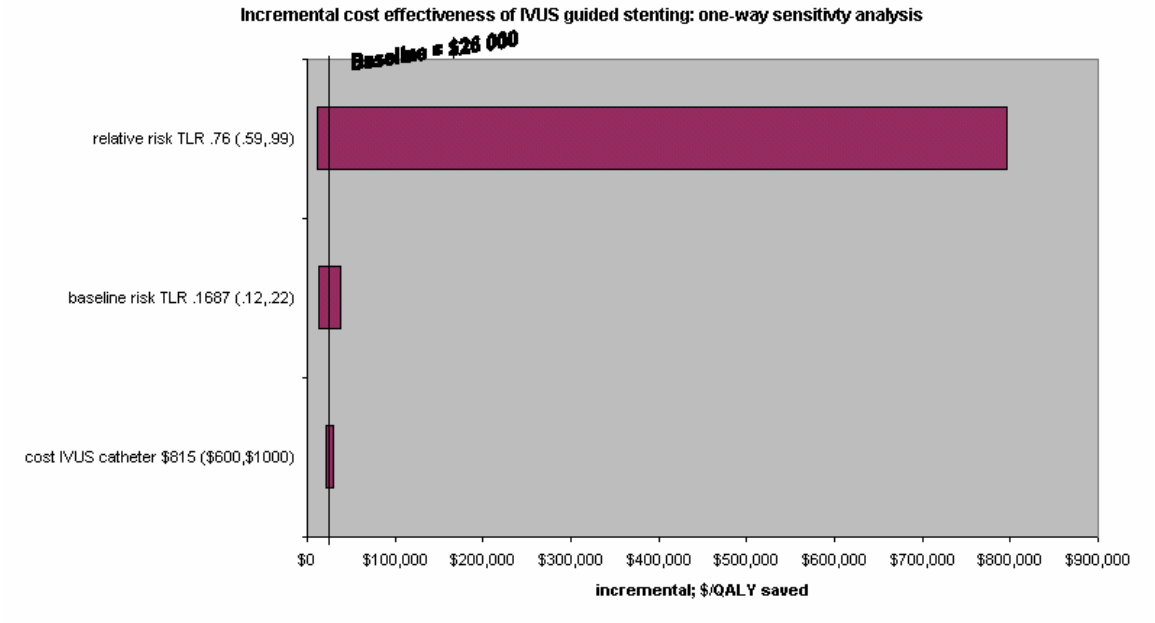


Figure 19 Incremental cost effectiveness of IVUS guided stenting: one way sensitivity analysis



Appendix F Cost estimates

Potential annual costs and benefits of adopting IVUS.

Based on an extra cost of each IVUS procedure of $1360, with $307 per patient in follow-up treatment costs avoided on average

Number of stent placements with angioplasty:

Data from application (AIHW data): 6457/8377 public, 4877/6038 private

NHCDC data: 6067/7931 public, 3158/4107 private

Using the AIHW data potential cost of all IVUS stent insertions (assuming total number does not change with procedure) = extra cost of treatment less cost of follow-up prevented:

Potential extra cost of treatment: $1360/ procedure*11334 potential procedures

= $15.41 million

Associated with this would be an anticipated reduction in follow-up costs (reduced TLR but increased MI) of: $307/procedure*11334 potential procedures

= -$3.48 million

Therefore net potential costs anticipated: ($1360-307)*11334= $1053*11334

= $11.93 million ($15.41-$3.48 million)

Potential net number of TLR cases prevented applying reduction from meta-analysis of 16.87% in control to 12.82% with IVUS: 0.0405*11334

=459 fewer cases of TLR annually

In summary if all public and private hospital stent placements were IVUS guided the procedure is estimated to cost the Australian health system $15.4 million of which it is estimated $3.5 million would be offset by reduced revascularisation costs. It is estimated the net $11.9 million would prevent approximately 460 target lesion revascularisations (140 CABG, 320 PTCA).

Abbreviations

Acc	Accuracy
AIHW	Australian Institute of Health and Welfare
ARTS	Arterial Revascularization Therapy Study (Trial)
AS	Area stenosis
AVID	Angiography Versus Intravascular ultrasound Directed stent placement (Trial)
CABG	Coronary artery bypass graft
CFR	Coronary flow reserve
CI	Confidence interval
CRUISE	Can Routine Ultrasound Influence Stent Expansion (Trial)
CSA	Cross-sectional area
CSN	Cross sectional narrowing
DRG	Diagnosis-related Groups
DS	Diameter stenosis
ECG	Electrocardiogram
ESC	European Society of Cardiology
FFR	Fractional flow reserve
GSM	Grey Scale Median
HIC	Health Insurance Commission
ICER	Incremental cost-effectiveness ratio
ICUS	Intracoronary ultrasound
IVUS	Intravascular ultrasound
ITT	Intention-to-treat
LMCA	Left main coronary artery
MACE	Major adverse cardiac events
MI	Myocardial infarction
MLA	Minimal lumen area
MLD	Minimum lumen diameter
NCCHTA	UK National Coordinating Centre for Health Technology Assessment
NPV	Negative predictice value
OR	Odds ratio
PPV	Positive predictive value
PTCA	Percutaneous transluminal coronary angioplasty
QALY	Quality adjusted life year
QCA	Quantitative coronary angiography
RCT	Randomised controlled trial
RESIST	RESstenosis after IVUS guided Stenting (Trial)
ROC	Receiver Operator Characteristic
RR	Relative risk
RR	Relative risk
SIPS	Strategy for Intercoronary ultrasound-guided PTCA and Stenting (Trial)
Sn	Sensitivity
Sp	Specificity
SPECT	Single photon emission computed tomography
TLR	Target lesion revascularisation
TVR	Target vessel revascularisation
YLD	Years of life with disability
YLL	Years of life lost

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