Coronary pressure wire

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Assessment report

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the 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.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Robert Weir, Dr Shelagh Dawson, Mrs Sarah Hogan, Mrs Susan Bidwell and Dr Ray Kirk from NZHTA, University of Otago. The report was edited by Carol Webb. The report was endorsed by the Minister for Health and Ageing on 28 March, 2006.

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Measurement of fractional flow reserve (FFR) and coronary flow reserve (CFR) is performed in the cardiac catheter laboratory when evaluating the need for percutaneous coronary intervention (PCI) and when evaluating the effectiveness of the intervention. The rationale for measuring FFR and CFR is to help reduce the uncertainty in management of patients with intermediate coronary lesions on angiography. While it may be clear how to proceed for coronary lesions with a diameter stenosis greater than 70 per cent or less than 30 per cent, there is uncertainty about how best to proceed when the diameter stenosis is between 30 and 70 per cent.

The scope of this evaluation includes the measurement of FFR and CFR for single or multi-vessel coronary artery disease. There are two specific indications:

1. Measurement of intermediate lesions (coronary artery stenosis of 30-70%).

2. Measurement post angioplasty/stenting.

The measurement is performed by inserting a specifically developed wire in the relevant coronary artery. Measurement is performed at maximum hyperemia (maximum coronary vasodilation).

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the 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 evidence is thus the basis of decision making when funding is sought under Medicare. A team from the New Zealand Health Technology Assessment (NZHTA) Research Unit was engaged to conduct a systematic review of literature on coronary pressure wire. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of coronary pressure wire

The review questions for (1) measurement of FFR and CFR in patients with an intermediate lesion on coronary angiography and (2) measurement of FFR and CFR in patients who have received percutaneous transluminal coronary angioplasty (PTCA) and/or stenting were:

- What is the safety of using a coronary pressure wire for the measurement of FFR and CFR?
- Does the use of a coronary pressure wire for the measurement of FFR and CFR improve diagnostic accuracy?
- Does the use of a coronary pressure wire for the measurement of FFR and CFR change patient management?
- Does the use of a coronary pressure wire for the measurement of FFR and CFR improve patient outcome?
- What is the cost-effectiveness of using a coronary pressure wire for the measurement of FFR and CFR?
- What is the clinical need for using the coronary pressure wire for the measurement of FFR and CFR?

Clinical need

Self-report data from the 2001 National Health Survey estimated that 355,600 (1.9% of the total population) Australians had coronary heart disease (CHD). During 2001-02 there were an estimated 48,700 CHD deaths or hospitalisations among 40-90 year olds in Australia. The age-standardised incidence of CHD fell by about 25 per cent during the period (Australian Institute of Health and Welfare (AIHW) and National Heart Foundation of Australia, 2004). In 2002-03, coronary heart disease accounted for 161,796 hospital separations in Australia. The majority of these were attributed to angina pectoris, with 83,212 ascribed to this cause.

During 2001-02, there were 23,982 PTCA procedures, including 21,917 with stenting, and 16,275 coronary artery bypass grafts in Australia. During the period 1993-4 to 2000, the rate of percutaneous interventions (PTCA and/or stenting) doubled while the rate of CABG operations declined.

Safety

Twenty six studies, involving 2639 participants, were identified that met the eligibility criteria for the safety component of the review. These studies were selected on the basis of FFR and/or CFR being measured and where safety concerns were related to the use of vasodilating agents to achieve maximal hyperemia and to the instrumentation required to measure FFR and CFR.

The great majority of adverse effects reported were self limiting in nature. There was one episode of severe bronchospasm. Two type B coronary dissections were also reported, but these adverse events did not require any specific intervention. Therefore, the measurement of FFR was associated with a satisfactory safety profile.

Effectiveness

Indication 1: Measurement of FFR and CFR in patients with an intermediate lesion on coronary angiography

There were four groups of studies: randomised controlled trials, comparison of FFR with a reference standard (the "triple stress test"), non-randomised studies following patients divided into groups according to FFR level, and non-randomised studies that followed patients with specified FFR levels. The RCTs provided the most reliable design.

One RCT compared a stress test strategy with an FFR measurement strategy in a population of patients with unstable angina or non-ST segment elevation MI (myocardial infarction) and did not find any significant difference in outcome between the two strategies. However, this study had a small sample size. The other RCT randomised the group of patients with FFR ≥ 0.75 to either receive (perform group) or not receive (defer group) PTCA. The participants with FFR < 0.75 all received PTCA. There was a significantly higher proportion of patients free from angina at 24 months in the defer group than in the perform group ($P = 0.02$), although there was no overall difference in event-free survival between these two groups. However, there was a significant difference in the event-free survival between the defer group and the group with an FFR < 0.75 (defer group: 89% versus group with FFR < 0.75: 78%, $P = 0.03$). This latter study provided the most reliable data.

The sensitivity and specificity of FFR compared with the reference standard of the "triple stress test" were 87.5 per cent (95% CI 67.6-97.3) and 100 per cent (95% CI 83.9-97.3) respectively. However, caution needs to be applied in interpreting the results of this study since the reference standard is unlikely to be of perfect sensitivity and specificity.

The other two groups of studies provided less reliable data given the limitations of the study designs used.

Overall, there was high-level evidence supporting the use of FFR in patients with single lesion disease in determining whether to proceed or defer coronary intervention at the time of angiography. It was less clear from this high-level evidence whether FFR measurement was more effective than stress testing. However, there were data supporting FFR having similar accuracy to stress testing and that the measurement of FFR results in change in management.

Indication 2: Measurement of FFR and CFR in patients who have received PTCA and/or stenting

Only four studies were identified that met the eligibility criteria for this indication. Three were registry-based studies that did not incorporate any change in management in association with an adverse FFR measurement. The fourth compared using FFR

measurement to guide further stenting with a strategy of directly stenting without measuring FFR in a non-randomised design.

There was no significant difference in survival at 700 days in this study, but it had only 155 participants. In the other three studies, a low FFR was associated with increased risk of subsequent cardiac events. However, it was unclear if a measurement of FFR would improve health outcomes among those with low FFR levels. This limitation was due to the lack of change in management within the study designs.

Cost-effectiveness

Cost-minimisation analysis was used to identify the most cost-effective strategy. This was because the overall conclusion of the effectiveness section was that currently available evidence on FFR measurement prior to a percutaneous intervention (PCI) procedure suggests there would be no difference in patient outcomes whether FFR measurement was used, stress testing was used, or patients proceed directly from angioplasty to PCI. Costs were estimated based on currently available cost data, including Medicare Benefits Schedule reimbursement fees, AR-DRG data for public and private hospitals, and the manufacturer's price for Radi pressure wire, which is used for FFR measurement. Cost estimates were based on a single lesion per patient.

The expected cost per patient, and therefore total annual costs, are expected to be lower for a strategy of stress testing prior to a decision to proceed with PCI than for a strategy of FFR measurement prior to a decision to proceed with PCI. The difference, however, is small and the resulting cost-effectiveness ratio is likely to be similar for the two strategies. Both of these strategies are expected to be associated with significantly lower cost-effectiveness ratios than a strategy of proceeding directly to PCI.

The expected total annual cost of performing FFR measurement on all 8,862 patients identified as having intermediate lesions on angiography annually is $66,610,620. This represents annual savings of $4,413,080 relative to performing stress testing on all patients. This amount is small compared with the expected annual savings associated with the use of FFR measurement instead of proceeding directly to PCI ($21,213,049). Due to a lack of evidence regarding the use of FFR measurement in patients who have received PCI, only a basic costing was estimated. Estimates are for patients with intermediate and severe coronary stenoses. For patients with intermediate coronary stenoses, the estimate is of the incremental direct cost of FFR measurement immediately following a PCI procedure. This assumes that FFR would also have been measured prior to PCI and that the same pressure wire may be re-used for FFR measurement following PCI. The total incremental cost per patient of measuring FFR following PCI for patients with intermediate coronary stenoses would be $250. Patients with severe coronary stenoses would not typically have had FFR measurement prior to PCI. For these patients, the use of coronary pressure wire may replace the use of a standard guidewire. The incremental direct cost per patient with severe coronary stenosis is estimated to be approximately $1,360.

Recommendations

1st indication

On the strength of evidence relating to safety, effectiveness and cost-effectiveness, the MSAC recommends that public funding be supported for the use of coronary pressure wires to determine whether revascularisation should be performed on intermediate lesions identified on coronary angiography, where previous stress testing has either not been performed or the results are inconclusive.

2nd indication

On the basis of the limited evidence relating to effectiveness and cost-effectiveness, the MSAC recommends that public funding not be supported for the use of coronary pressure wires to assess the effectiveness of percutaneous coronary interventions.

-The Minister for Health and Ageing accepted these recommendations on 28 March, 2006 -

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of coronary pressure wire, which is a diagnostic test for the measurement of fractional flow reserve (FFR) and coronary flow reserve (CFR). FFR and CFR are used in the diagnosis, measurement and evaluation of coronary artery stenosis or restenosis. This review has considered all devices that are used in the measurement of FFR and devices that use similar technology to Radi pressure wire™ in the measurement of CFR.

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 FFR and CFR measured using thermodilution techniques for the diagnosis, measurement and evaluation of coronary artery stenosis or restenosis.

Background

Clinical problem

Coronary heart disease results from coronary atherosclerosis. Atherosclerosis results in plaque build-up with subsequent coronary stenosis, reducing blood flow to the heart. Such blockages can produce myocardial infarction and angina. Current treatment strategies include risk factor modification, medical therapy to treat angina and revascularisation by percutaneous transluminal coronary angioplasty (PTCA), stenting or coronary artery bypass surgery (CABG). Clinical management is partially guided by coronary angiography. In patients with severe stenotic lesions on coronary angiography (diameter stenosis > 70 per cent), revascularisation may be indicated. In patients with mild stenotic lesions (diameter stenosis < 30 per cent), revascularisation is not indicated. However, the management of patients with intermediate coronary stenoses (30-70 per cent) is less certain. The measurement of FFR and CFR potentially assists with determining the most appropriate management strategy in the group of patients with intermediate lesions.

Coronary stenosis is currently detected by a combination of angiography and stress testing. Coronary pressure wires measure the FFR and CFR as part of the angioplasty procedure. FFR provides a physiological measure of the extent to which a lesion limits blood flow. It also provides an index to monitor and guide coronary intervention. FFR refers to the maximum achievable blood flow to the myocardium, supplied by a stenotic artery, as a fraction of normal maximum flow. CFR refers to the ratio of hyperemic flow to resting flow for a given coronary artery.

FFR has several theoretical advantages over CFR. Firstly, CFR is unable to discriminate between epicardial disease, microvascular disease or a combination of both whereas FFR is a specific index for the epicardial stenosis. Therefore, FFR is a better indicator of the extent to which a patient can be helped by revascularisation. Secondly, FFR is independent of changes in heart rate, blood pressure and contractility. It takes into account the contribution of collateral flow and since there is no need for a normal reference artery, it can be applied in multivessel disease and for multiple lesions within a single vessel (Pijls et al., 2000). The rationale for the measurement of FFR is shown in Figure 1.

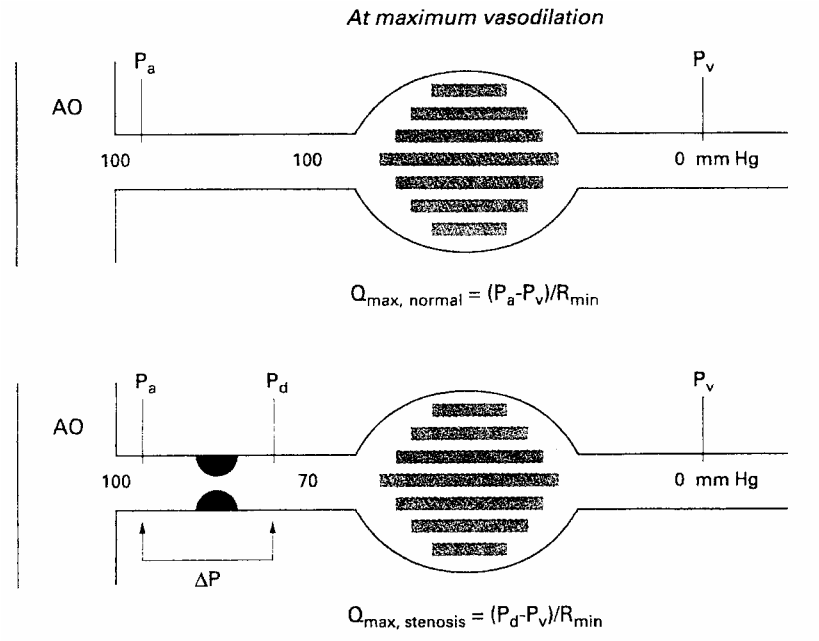


Figure 1 **Schematic diagram of coronary arteries, with and without stenosis, and its myocardial vascular bed**

(Reproduced with permission from the BMJ Publishing Group. *Heart*, 1998; 80; Oiljs NJJ and De Bruyne B, Fig 1, p 539.)

The top diagram in Figure 1 represents the absence of stenosis whereas the bottom diagram represents a coronary artery stenotic lesion. Myocardial blood flow is the perfusion pressure across the myocardium, divided by the myocardial resistance. At maximum vasodilatation, resistance is minimal (R_{min}). In the absence of stenosis, pressure across the myocardium is $P_a - P_v$, whereas in the presence of a stenosis the pressure across the myocardium has decreased to $P_d - P_v$. Therefore, FFR is:

$FFR = [(P_d - P_v)/R_{min}]/ [(P_a - P_v)/R_{min}]$ (Pijls et al., 2000).

However, at maximum coronary vasodilation (hyperemia) and in the absence of high venous pressure this simplifies to:

$FFR = P_d/P_a$.

There are criticisms of the FFR theory. Firstly, several authors contradict the central tenet that myocardial resistance is constant at maximum vasodilatation with and without stenosis. Ignoring change in myocardial resistance tends to overestimate the FFR. Secondly, raised venous pressure is ignored, which would also overestimate FFR (Bishop and Samady, 2004).

Resting myocardial blood flow remains normal until the epicardial coronary arteries are stenosed at least 85 per cent by diameter, and hyperemic blood flow reduces when the stenosis is at least 55 per cent by diameter (Gould et al., 1974). Hyperemic blood flow represents an excess of blood resulting from vasodilatation. CFR, defined as the ratio of hyperemic flow to resting flow for a given artery, decreases with increasing severity of the stenosis. CFR reflects both epicardial and microvascular resistance and is affected by a number of factors, including age, left ventricular hypertrophy, diabetes mellitus and myocardial infarction. Other difficulties include variability in measurement with

haemodynamic changes, overlap between normal and abnormal levels and technical difficulties. Relative CFR attempts to overcome these difficulties by measuring CFR in the index vessel and comparing it with that in an adjacent non-obstructed vessel. However, this requires the presence of a normal vessel (Bishop and Samady, 2004).

The applicant in this review proposes the following benefits for incorporation of a coronary pressure wire for the measurement of FFR and CFR into an angioplasty procedure:

1. Used as a diagnostic tool it assesses the significance of coronary artery stenosis and/or restenosis and therefore enables more accurate decisions about treatment. A FFR $\geq$ 0.75 would indicate that angioplasty and stenting is not necessary.

2. If angioplasty and stenting are indicated, the same pressure wire is used as part of the procedure rather than the standard guidewire.

3. The pressure wire can also be used after the angioplasty and stenting procedures to evaluate the effectiveness of the intervention.

4. The pressure wire can identify culprit lesions in multivessel disease or diffuse lesions, resulting in deferment of by-pass surgery or a selective PTCA of the culprit lesion/s being performed versus the alternative of CABG for all vessels. It is controversial whether complete CABG is superior to PTCA of culprit lesions only and PTCA is less invasive than CABG.

The technique is to be performed in the catheterisation laboratory by interventional cardiologists. Clinical flowcharts are included in Appendix C that outline the potential role of coronary pressure wire for the measurement of FFR and CFR in clinical practice.

The procedure

Measurement of FFR and CFR is performed in the cardiac catheter laboratory when evaluating the need for percutaneous coronary intervention (PCI) and when evaluating the effectiveness of the intervention.

As an example, for Radi pressure wire™ an intravascular PressureWire Sensor™ is used in the real-time calculation of FFR and this sensor is upgradeable to enable the additional measurement of CFR and sensor-tip temperature measurements. The RadiAnalyzer™ interface can be connected to a regular monitoring system so that waveforms can be shown on the monitor. A RadiView™ software kit is available to transfer recordings from the RadiAnalyzer™ to the catheter laboratory PC or printer and this software can be upgraded to include temperature and CFR measurements. CFR is measured by thermodilution methods.

The WaveWire™ is also designed to measure FFR. WaveMap™ software allows automatic calculation of pressure gradients and WaveMap Revision H™ software allows interfacing with catheter laboratory monitoring systems, without an aortic signal output.

The scope of this evaluation includes the measurement of FFR and CFR for single-vessel or multi-vessel coronary artery disease.

There are two specific indications:

1. Measurement of intermediate lesions (coronary artery stenosis of 30-70%).

2. Measurement post angioplasty/stenting.

Measurement is performed at maximum hyperemia (maximum coronary vasodilation).

Indication 1 includes two benefits identified by the applicant: (1) use as a diagnostic tool to assess the significance of coronary artery stenosis/re-stenosis, and (2) the ability to identify culprit lesions in multi-vessel disease or diffuse lesions. The use of the same pressure wire rather than a standard guidewire as part of the angioplasty/stenting procedure (benefit 2 listed earlier) was not viewed as an indication for this review by the Advisory Panel.

Clinical need/burden of disease

Coronary heart disease (CHD) is the largest single cause of death and the most common cause of sudden death in Australia. In 2002, there were 26,023 deaths due to CHD (19.5% of all deaths). Self-report data from the 2001 National Health Survey estimated that 355,600 (1.9% of the total population) Australians had CHD. The age-standardised incidence of CHD fell by about 25 per cent during the period (Australian Institute of Health and Welfare (AIHW) and National Heart Foundation of Australia, 2004).

The age-standardised prevalence of CHD was one third higher among males than females in the National Health Survey. High blood pressure (50%) and high blood cholesterol (38%) were commonly reported risk factors (Australian Institute of Health and Welfare (AIHW) and National Heart Foundation of Australia, 2004).

Hospitalisation

During the period 1993-4 to 2001-2 the age-standardised rate of hospitalisation increased by 12 per cent. Age-standardised rates of hospitalisation were approximately twice as high among Aboriginal and Torres Strait Islanders compared with other Australians during 2001-2 (Australian Institute of Health and Welfare (AIHW) and National Heart Foundation of Australia, 2004).

Males were twice as likely to be hospitalised for CHD as females during 2001-2. Most admissions occurred in older Australians. For example, the rate of hospital use for acute MI among those aged 75 years and over was almost twice as high as that in 65-74 year olds and more than three times as high as that for 55-64 year olds (Australian Institute of Health and Welfare (AIHW) and National Heart Foundation of Australia, 2004).

In 2002-03, ischaemic heart disease accounted for 161,796 hospital separations in Australia. The majority of these (83,212) were attributed to angina pectoris, compared with 43,767 attributed to acute myocardial infarction, 349 to subsequent myocardial infarction, 29 to complication following myocardial infarction, 520 to other ischaemic heart disease and 33,919 to chronic heart disease. There were 105,418 separations for these codes among males and 56,377 among females during the 2002-3 period (Australian Institute of Health & Welfare (AIHW), 2004).

Mortality

Deaths from CHD by population subgroup is shown in Table 1 (Australian Institute of Health and Welfare (AIHW) and National Heart Foundation of Australia, 2004).

Table 1 CHD death by population group

Year	Population subgroup	Males	Females	Persons
		Number per 100,000 population		
2002	**Age group (years)**			
	45-54	56.4	10.5	33.4
	55-64	155.5	42.3	99.5
	65-74	452.6	184.5	314.6
	75-84	1,307.3	797.9	1,013.3
	85+	4,050.3	3,296.6	3,531.4
2000-02	**Socioeconomic status**			
	1st quintile (most disadvantaged)	193.3	114.9	150.4
	2nd quintile	185.4	106.4	142.3
	3rd quintile	179.5	104.1	137.8
	4th quintile	163.0	97.6	126.9
	5th quintile (least disadvantaged)	154.7	89.3	116.6
2000-02	**Aboriginal and Torres Strait Islander status** Standardised mortality ratio	2.9*	2.5*	2.6*
2000-02	**Region**			
	Major cities	169.4	99.0	129.7
	Regional	185.3	107.8	143.2
	Remote	186.0	120.2	155.1

* Statistically significantly higher than 1.0 (other Australians)

Coronary procedures

There were 38,901 coronary revascularisation procedures (PCI and CABG) performed in 2000, including 21,784 PCI procedures and 17,117 CABG operations. From 1993-4 to 2000 the age-standardised coronary revascularisation rates increased by 30 per cent. However, the PCI rates doubled in that time period, while there was a decline in the rate of CABG operations. (See Figure 2 for details of the changing rate of CABG and PCI since 1990). The median length of stay in hospital was 9.0 days in 2000 for CABG operations, which contrasted with 2.0 days for PCI. The in-hospital mortality rate for PCI procedures in 2000 was 0.9 per cent. The proportion of PCI procedures involving stent insertion had also increased since the mid 1990s. In 1995 coronary stents were inserted in 30 per cent of PTCA procedures compared with 90 per cent by 2000 (Australian Institute of Health and Welfare (AIHW), 2003). No data was identified that allowed estimation of the proportion of intermediate stenoses stented in Australia. Table 2 shows the number of coronary procedures in Australia for the period 2002-03. Of the 88,618 coronary angiographies performed, 39,654 (45%) were performed in a public hospital (Australian Institute of Health & Welfare (AIHW), 2004).

Table 2 Number of coronary procedures in Australia, 2001-02

Procedure	Procedure block	Total number of procedures
Coronary angiography	668	81,926
Percutaneous transluminal coronary angioplasty (PTCA)	670	23,982
Stenting*	671	21,917
Coronary artery bypass graft	672-679	16,275

* These form a subset of the PTCA procedures

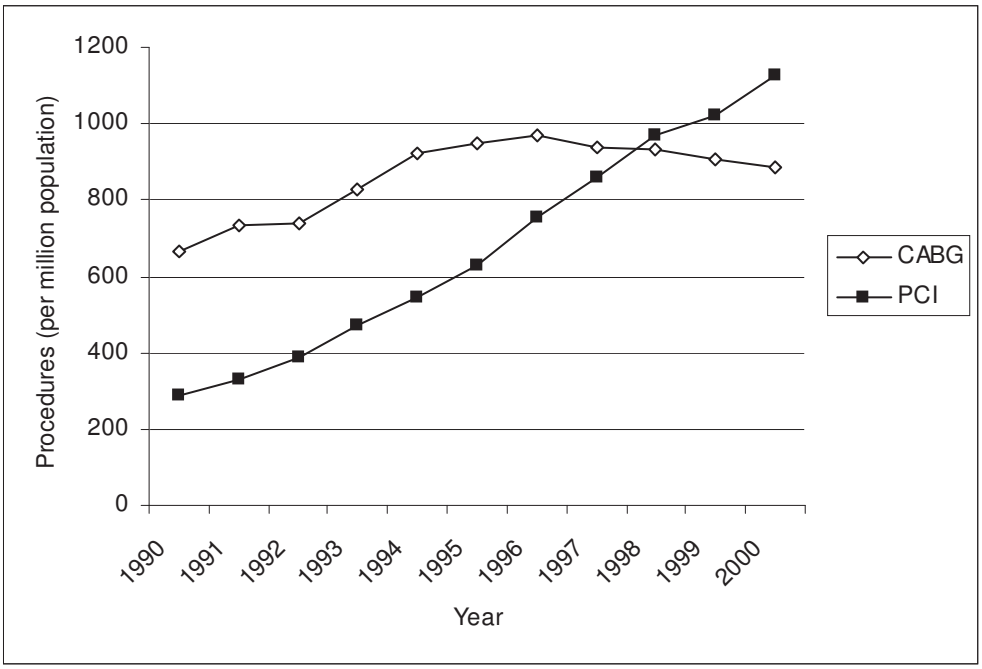


Figure 2 Coronary artery bypass grafts and percutaneous coronary interventions, 1990-2000

Cost of CHD

Coronary heart disease has been estimated to be the highest cost individual disease in Australia, consuming 3 per cent of the total health system expenditure. In 2000-01, $1,466 million dollars was spent on CHD with 72 per cent of that cost coming from hospitals, 14 per cent from pharmaceutical costs and 9 per cent from out of hospital medical expenses (Australian Institute of Health and Welfare (AIHW), 2004).

Assessment of test effectiveness

Three factors are considered necessary to determine the effectiveness of a diagnostic test:

- accuracy of the test, ie, the diagnostic performance;
- change in patient management as a consequence of the diagnostic test result;

- effectiveness of the change in patient management.

Diagnostic test performance

In the context of this review, diagnostic performance represents the accuracy of test measurements. Usually it is examined by estimating the validity (sensitivity, specificity and positive and negative likelihood ratios) and reliability of the test. Alternative measures are appropriate in tests producing continuous, quantitative data.

Change in patient management

A test has therapeutic impact if the treatment decision is changed as a result of the information provided by the test. Possible changes are that new therapy is added or the need for therapy is averted, or therapy is modified.

Patient health outcomes

The ultimate goal of diagnostic testing is to contribute to improvement in the health of patients. If a diagnostic test is to be beneficial, the diagnostic test performance needs to be satisfactory, the diagnostic test results should have an impact on therapy, and the therapy should be effective.

Comparators

The comparator was selected based on the test used most frequently in current practice in Australia. In patients being assessed for intermediate coronary artery lesions the comparators were stress testing by:

- exercise ECG;
- stress myocardial perfusion imaging including stress thallium;
- stress echocardiography.

The economic analysis examining the use of FFR measurement in patients with intermediate coronary lesions also included, as a comparator, direct stenting without recourse to stress testing or FFR measurement.

In patients being evaluated following balloon angioplasty and/or stenting the comparator was balloon angioplasty and/or stenting without pressure wire.

Reference standard

The reference standard included measures of patient outcome and measures of myocardial ischaemia. The patient outcome measures were:

- all-cause mortality;
- cardiac-related mortality;

- myocardial infarction;
- angina;
- coronary artery revascularisation;
- quality of life.

The "triple stress test" (exercise ECG, stress myocardial perfusion imaging including stress thallium, and stress echocardiography) was used as the reference standard for myocardial ischemia. Myocardial ischaemia was classified as present if at least one of the three stress tests was positive.

Existing procedures

The following procedures are currently listed on the MBS schedule:

- Selective coronary angiography (MBS item numbers 38215, 38218, 38220, 38222, 38225, 38228, 38231, 38234, 38237, 38240, 38243, 38246, 59925);
- Transluminal balloon angioplasty (MBS item numbers 35304 and 35305);
- Transluminal stent insertion including associated balloon dilatation for coronary artery (MBS item number 35310);
- Single stress or rest myocardial perfusion study (MBS item numbers 61302 and 61303);
- Combined stress and rest myocardial perfusion study (MBS item numbers 61306 and 61307);
- Exercise ECG (MBS item number 11712).

Marketing status of the device/technology

Both the Radi pressure wire™ and the WaveWire™ are listed on the Australian Register of Therapeutic Goods with the Therapeutic Goods Administration.

Current reimbursement arrangement

Currently, the use measurement of FFR and CFR is not funded under the Medicare Benefits Scheme. Table 3 lists relevant procedures currently funded under the November 2004 edition of the Medicare Benefit Scheme (Australian Department of Health & Ageing, 2004).

Table 3 Current procedures funded under the Medical Benefits Scheme

Codes	Procedure	Fee
11712	Exercise ECG	$129.05
35304-35305	Transluminal balloon angioplasty	$437.35-$560.70
35310	Transluminal stent insertion	$646.90
38215-38246,59912, 59925	Selective coronary angiography	$188.20 - $1129.10
61302-61303	Single stress or rest myocardial perfusion study	$444.40-$559.70
61306-61307	Combined stress and rest myocardial perfusion study	$702.65-$826.65

Approach to assessment

Review of literature

The medical literature was searched by an Information Specialist to identify studies and systematic reviews examining the diagnostic utility of coronary pressure wire for the measurement of FFR and CFR. Searches were updated in December 2004. Searches were conducted using the following sources:

- Medline
- Embase
- Current Contents
- Science Citation Index
- Cochrane Library (Systematic Reviews & Controlled Trials Register)
- NHS Centre for Reviews and Dissemination databases (DARE, HTA, NHS EED)
- Website sources as detailed in Appendix D.

Search strategy

The search strategies used to identify relevant papers are outlined in Appendix E.

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (National Health and Medical Research Council, 2000).

These dimensions (Table 4) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect, and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 4 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 5

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 5.

Table 5 Designations of levels of evidence*

Level of evidence	Study design
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 pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or 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/post-test

*Modified from (National Health and Medical Research Council, 1999).

Eligibility criteria

The eligibility criteria for inclusion of studies in the effectiveness component of the review are shown in Table 6.

The assessment of safety used the same methods as the assessment of effectiveness except that studies with fewer than 15 participants were included.

Table 6 Inclusion/exclusion criteria for identification of effectiveness studies

Characteristic	Criteria
Inclusion criteria	
Publication type	Clinical studies using human subjects.
Patients	Patients being assessed for coronary stenosis and restenosis or being evaluated following percutaneous transluminal coronary angioplasty (PTCA) and/or stenting of coronary artery stenosis or restenosis
Sample size	At least 15 human patients were tested by FFR or CFR
Intervention/test	FFR measurement at maximal coronary vasodilation following intravenous or intracoronary adenosine/ATP or intracoronary papaverine CFR measurement using thermodilution/temperature sensor methods at maximal coronary vasodilation following intravenous or intracoronary adenosine/ATP or intracoronary papaverine.
Comparator	Indication 1: stress testing Indication 2: PTCA/stenting without pressure wire
Outcome	All-cause mortality, cardiac-related mortality, myocardial infarction, angina, coronary artery restenosis, CABG, PTCA/stenting, readmission for a coronary event, quality of life, measures of myocardial ischaemia
Exclusion criteria	
Publication type	Non-systematic reviews, letters, editorials, expert opinion articles, conference proceedings, comments and articles published in abstract form.
Reference standard	Studies of diagnostic accuracy were excluded if they did not use the "triple stress test" as the reference standard
Publication superseded	Publication superseded by a later publication with longer follow-up data and overlap in the patient population
Language	Non-English language articles

Review methods

Selection of studies for appraisal

Studies were selected for inclusion by two independent reviewers if they fulfilled the eligibility criteria. Agreement on studies for inclusion was reached by discussion and, if necessary, third-party arbitration. Level of agreement in selection was estimated using kappa coefficients.

Level and quality of the evidence in identified studies

The evaluation classified studies according to National Health and Medical Research Council (NHMRC) dimensions of evidence and levels of evidence criteria (see Tables 4 and 5). High-level evidence for indication 2 (measurement post angioplasty/stenting) would be provided by a randomised-controlled trial comparing percutaneous transluminal coronary angiography (PTCA) with coronary pressure wire for the measurement of FFR and CFR with PTCA alone. The test results would be used to develop treatment strategies for the participants. Clinical outcomes would then be obtained. In addition to the NHMRC levels of evidence, further grading of studies for

diagnostic accuracy was conducted as shown in Table 7. This was adopted for any studies that evaluated coronary pressure wire for the measurement of FFR and CFR against a reference standard.

Table 7 Grading system for the appraisal of included studies of diagnostic accuracy

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed to avoid bias? High quality = no potential for bias based on predefined key criteria Medium quality = some potential for bias in areas other than those pre-specified as key criteria Poor quality = potential for bias based on key pre-specified criteria	Q1 high quality Q2 medium quality Q3 poor quality or insufficient information

The data extraction tool used for this review is shown in Appendix F. Standard criteria were used for the assessment of study quality and potential for bias.

The quality of studies selected for assessment of diagnostic accuracy was evaluated using the criteria shown in Table 8. The quality of studies was classified as follows:

- Level of evidence I = high quality (Q1);
- Level of evidence II and III = medium quality (Q2);
- Level of evidence IV = poor quality (Q3).

Table 8 Susceptibility to bias

Level of evidence	Criteria
I	Independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard.
II	Independent, blind or objective comparison but in a set of non-consecutive patients, or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the diagnostic test and the reference standard.
III	Independent blind comparison of an appropriate spectrum, but the reference standard was not applied to all study patients.
IV	Any of: Reference standard was not applied blinded or not applied independently. No reference test applied (case series)

Outcomes to be evaluated

Three categories of outcome were evaluated in this systematic review. They were:

1. Diagnostic test performance. Diagnostic test performance was assessed by comparing the performance of FFR and CFR against the comparators selected, using the "triple stress test" as the reference standard.

2. Therapeutic impact. FFR and CFR were considered to have therapeutic impact if the treatment decision was changed as a result of information provided by the result.

3. Patient health outcomes. The ultimate goal of diagnostic testing is to contribute to improvement in the health of patients. Randomised controlled trials are the best design for answering this question. Outcome measures previously listed were used for such studies.

Assessment against primary outcomes

The effect of FFR and CFR was compared with the selected comparators where possible, using appropriate measures of effect and depending on the extent of information provided in the study articles selected for appraisal.

Subgroups of interest

Subtopics of interest included:

- single lesion disease;
- left main coronary artery disease;
- multiple lesion disease: single vessel and multi vessel;
- diffuse lesions.
- transplant vasculopathy;
- myocardial infarction;
- unstable angina;
- left ventricular dysfunction;
- left ventricular hypertrophy;
- microvascular disease;
- diabetes;
- hypertension;

Expert advice

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

Results of assessment

Research questions

There were two indications considered for the measurement of FFR and CFR in this review:

1. Measurement of FFR and CFR in patients with an intermediate lesion on coronary angiography.

2. Measurement of FFR and CFR in patients who had received PTCA and/or stenting.

The review questions for (1) measurement of FFR and CFR in patients with an intermediate lesion on coronary angiography, and (2) measurement of FFR and CFR in patients who have received percutaneous transluminal coronary angioplasty (PTCA) and/or stenting were:

- What is the safety of using a coronary pressure wire for the measurement of FFR and CFR?

- Does the use of a coronary pressure wire for the measurement of FFR and CFR improve diagnostic accuracy?

- Does the use of a coronary pressure wire for the measurement of FFR and CFR change patient management?

- Does the use of a coronary pressure wire for the measurement of FFR and CFR improve patient outcome?

- What is the cost-effectiveness of using a coronary pressure wire for the measurement of FFR and CFR?

- What is the clinical need for using the coronary pressure wire for the measurement of FFR and CFR?

Papers selected for the review of safety and/or effectiveness

Articles that did not meet the selection criteria were excluded during an initial assessment of the abstracts. Ambiguous or unclear citations were included in the next assessment stage of examination in full text. Two reviewers independently examined each citation for inclusion. Discrepancies in selection were resolved by discussion and by re-examination of the relevant studies. A third reviewer was available in case of unresolved differences but third party arbitration was not needed. Only studies that successfully passed this process were included in this review. There was a high level of agreement between the two reviewers independently selecting studies for inclusion in the review (kappa = 0.97).

The search strategies detailed in Appendix D, along with additional papers supplied by the applicant, resulted in the scanning of 3,567 references in the course of the search and the retrieval of 176 papers in full text. Thirty-three articles were identified that met the eligibility criteria for the review and all were critically appraised. Details of the selection process are shown in Figure 3.

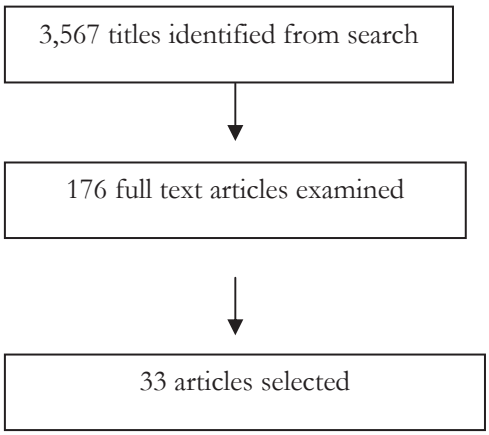


Figure 3 Study selection process for coronary pressure wire review

The reasons for exclusion of studies are detailed in Table 9. The *a priori* exclusion criteria were prioritised in the following order:

- sample size less than 15 for the effectiveness component of the review;
- animal study;
- FFR and CFR not measured;
- CFR measured but thermodilution methods not used;
- outcomes measures used not of interest;
- population group not relevant to the review;
- publication superseded;
- publication was a letter, abstract, commentary or editorial;
- non-English language article;
- non-systematic review.

When there was more than one reason for exclusion, the reason for exclusion that was highest on the above list was specified.

Table 9 Reasons for exclusion of studies from the review

Reason for exclusion	Number
n < 15	752
Animal study	175
FFR and CFR not measured	1,860
CFR measured but thermodilution methods not used	514
Outcomes measures used not of interest	80
Population group not relevant to the review	65
Publication superseded	2
Publication was a letter, abstract, commentary or editorial	15
Non-English language article	0
Non-systematic review	71
Total	3,534

Twenty-six studies were included in the safety component of the review, 19 were included in the effectiveness section, and two were included in the economics section.

Is it safe?

Safety concerns were considered in relation to the medication used to produce maximum hyperemia and also in relation to the instrumentation used to measure FFR and/or CFR. Medications used for inducement of hyperemia included:

- IV adenosine
- IC adenosine
- IV ATP
- IC ATP
- IV papaverine
- IC papaverine

There were 2,639 participants for which some comment about safety of the FFR or CFR measurement procedure, including use of agents to vasodilate coronary vessels, could be identified. In Australia, papaverine is currently on label for the treatment of erectile dysfunction but not for the vasodilation of coronary vessels.

The dosage used varied between studies and, in the case of intra-coronary administration, by coronary artery. Most studies reported no complications associated with the procedure. One episode of severe bronchospasm and an episode of severe nausea associated with IV adenosine was documented in one study. Other effects likely to be attributable to the vasodilating agents were self-limiting in nature.

Complications likely to be attributable to the instrumentation used for measurement of FFR and/or CFR were also reported. Two type B coronary dissections were described but neither required any specific intervention. One procedure had to be abandoned before FFR measurement due to severe chest pain.

More detail is provided in Appendix G.

Summary

There were 2,639 participants for which some comment about safety of the FFR and/or CFR measurement procedure could be identified. From those procedures, there were complications of a transient nature reported in a limited number of cases. No specific complications associated with long-term implications for the patient were reported. While there was variability in reporting, and some transient effects were likely to be unreported, the measurement of FFR and CFR was associated with a satisfactory safety profile. This included consideration of safety issues associated with agents used to induce hyperemia as well as the specific instrumentation required to estimate FFR and/or CFR.

Is it effective?

The use of FFR and CFR was considered both for patients with intermediate lesions on coronary angiography and patients who had received PTCA and/or stenting. However, data on the effectiveness of CFR measurement for both these indications was lacking. Therefore, CFR measurement was not considered further.

Indication 1: Measurement of FFR in patients with an intermediate lesion on coronary angiography

There were four general groups of studies selected for the review that examined the effectiveness of measuring FFR in patients with an intermediate lesion on coronary angiography:

1. Randomised controlled trials. Two studies were identified that had an RCT component in their methodology. In one study (Leesar et al., 2003), participants were randomised to receive either FFR measurement or stress testing. In the group with FFR ≥ 0.75 or a negative stress test, no further intervention was used. In the group with FFR < 0.75 or a positive stress test, percutaneous coronary intervention (PCI) was applied. In the second RCT (Bech et al., 2001a), participants were divided into three groups. The first group consisted of patients with an FFR < 0.75. All participants in this group had a PTCA. In the group with FFR ≥ 0.75, participants were randomised to either receive or not receive PTCA.

2. Comparison of FFR with the "triple stress test" as the reference standard. One study was identified that used the "triple stress test" as the reference standard (Pijls et al., 1996). The "triple stress test" consisted of the bicycle exercise test, thallium scintigraphy and dobutamine stress echocardiography. If any single test was positive, the "triple stress test" was considered to be positive. The "triple stress test" should be considered as an imperfect reference standard, since it is unlikely to be characterised by perfect sensitivity and specificity. Therefore, some caution is required in interpreting the results from this study since false positive and false negative FFR results may be due to the inadequacies of the reference standard rather than the FFR measurement.

3. Non-randomised studies following patients that were divided into groups based on their FFR level, with various interventions being determined by the FFR level. In general, participants with an FFR ≤ 0.75 received some form of coronary artery revascularisation, such as PTCA with or without stenting, whereas those with a level > 0.75 usually did not receive such an intervention. Thus, a FFR > 0.75 was considered functionally non-significant. The level of adverse events was compared between participants in these two groups to evaluate the policy of deferring intervention in the group with FFR > 0.75. However, this group of studies does not provide information on the proportion who would have experienced an adverse event in the group with an FFR > 0.75 if coronary artery revascularisation had been performed in this group.

4. Non-randomised studies that followed patients with specified FFR levels. The FFR level was greater than 0.75 in these studies and the participants did not receive any form of coronary artery revascularisation. This group of studies should therefore be considered as uncontrolled studies although they do provide some information about the level of adverse outcomes in patients with stenoses that were considered functionally non-significant.

There were also important differences in design among the studies included within each of the above four categories. Most importantly, the two randomised controlled trials examined different population groups, and the comparison group(s) differed between these studies. Characteristics of these studies are provided below.

Randomised controlled trials

Bech et al 2001

In this RCT, patients with a *de novo* stenosis of greater than 50 per cent in a native coronary artery were assigned to one of three groups (Bech et al., 2001a). Initially, participants were randomly assigned to either the "perform" or "defer" groups, referring to either having PTCA performed or not performed respectively. When FFR was measured, those with an FFR ≥ 0.75 were assigned to the 'perform' or 'defer' group based on the randomisation before FFR measurement. However, if the FFR was less than 0.75, all participants had PTCA performed irrespective of the earlier randomisation assignment. Therefore, the three groups were:

1. FFR ≥ 0.75, randomly assigned to perform: proceeded with PTCA (n=90);

2. FFR ≥ 0.75, randomly assigned to defer: did not proceed with PTCA (n=91);

3. FFR < 0.75: all proceeded with PTCA (n=144).

In this trial, an event was defined as mortality, MI or coronary artery revascularisation. There was no significant difference in event-free survival between the defer/FFR ≥ 0.75 and perform/ FFR ≥ 0.75 groups at 24 months (defer group: 89% versus perform group: 83%, $P = 0.27$) but there was a significant difference in the event-free survival between the defer/ FFR ≥ 0.75 group and the group with an FFR < 0.75 (defer group: 89% versus group with FFR < 0.75: 78%, $P = 0.03$). A significantly higher proportion of patients was free from angina at 24 months in the defer group than in the perform group ($P = 0.02$).

This study was characterised by a high follow up-rate at 24 months (98%), measurement of outcome was blind to group assignment and an intention-to-treat analysis was used. The age range of the participants was not stated, limiting knowledge about the spectrum of patients, although the average age was 60-61 years in the three groups. There was also no comparison between FFR measurement and stress testing.

Further details about this study are provided in Appendix G.

Leesar et al, 2003

In this RCT, participants with a single lesion of intermediate severity who had unstable angina or non-ST segment elevation MI were randomised to either the FFR group or the stress test group (Leesar et al., 2003). Each study arm had 35 participants. There were no significant differences in outcome between study groups (see Table 10).

Table 10 Results from RCT conducted by Leesar et al comparing FFR measurement with stress testing

Outcome measure	FFR group (%)	Stress testing group (%)
All cause mortality	0	0
Cardiac mortality	0	0
MI	3	3
CABG	6	3
PTCA	0	0
Readmission for unstable angina	14	17

There were limitations to the study. The low sample size was the most significant, resulting in a lack of power to detect a significant difference in outcome between the two study groups. The population was restricted to patients with unstable angina or non-ST segment elevation MI and the expert opinion of the Advisory Panel suggests this population is less likely to benefit from FFR measurement compared with other groups, such as patients with stable angina. The age range of participants was also not presented, thus the spectrum of patients was unclear. It was also unclear if the decision to either readmit for unstable angina or to proceed to CABG was made blind to the study group. However, the follow-up rate was high at 97 per cent in both groups with a mean follow-up of 14 months in the FFR group and 12 months in the stress test group. More details about this study are supplied in Appendix G.

Comparison between FFR and "triple stress test"

One study was identified that allowed a comparison between FFR and the "triple stress test" (Pijls et al., 1996). The "triple stress test" consisted of the bicycle exercise test, thallium scintigraphy and dobutamine stress echocardiography. If any single test was positive, the triple stress test was considered to be positive. The study had 45 participants, all of whom had an angiographically detectable stenosis of ~50 per cent in the proximal part of one major coronary artery. The study population had similar characteristics to that in the RCT by Bech et al. An FFR < 0.75 was taken as evidence of a functionally significant stenosis. The study results are shown in Table 11. In the group with FFR ≥ 0.75 there were no ischaemic events after a mean follow-up period of 14 months.

Table 11 Validity of FFR measurement when compared with the "triple stress test" as the reference standard

Outcome measure		
Sensitivity (%)	87.5	(95% CI 67.6-97.3)
Specificity (%)	100.0	(95% CI 83.9-100)
LR+*	∞	
LR-**	0.13	(95% CI 0.04-0.36)

*Positive likelihood ratio
**Negative likelihood ratio

This study was characterised by a comparison between FFR and the "triple stress test", but the blinding status between the four tests was unclear from the study description. The index test (FFR measurement) and the reference standard ("triple stress test"ing) were independent and there was no verification bias. However, the clinical data available to the investigators performing the tests was unclear. The greatest uncertainty in this study relates to the accuracy of the reference standard and it is not possible to be certain whether the estimated sensitivity of FFR (87.5%) reflects the imperfect reference standard or imperfect performance from measuring FFR. For example, if the reference standard was based on thallium scanning and stress echocardiogaphy alone, the estimated sensitivity for FFR measurement would have been 95.5 per cent (95% CI 77.2-99.9). Exercise testing is uncommonly used in routine clinical practice currently for this indication. It should also be noted that the diameter of the pressure wire used in this study was larger than is currently used (0.018" versus 0.014"). However, the expert opinion of the Advisory Panel is that this change in diameter is unlikely to have a significant effect on the measured FFR. Given the uncertainty over the validity of the reference standard, it is important to note there were no events in the group with FFR ≥ 0.75 over a mean follow-up period of 14 months.

Non-randomised studies following patients categorised by FFR level

In this group of eight studies, FFR was measured before any planned intervention, such as PTCA. In most studies, the intervention proceeded only in patients with an FFR < 0.75. The exception to this was one study where patients with an FFR < 0.75 proceeded to CABG and all other patients received PCI (Botman et al., 2004). One study also followed patients for one year without providing any form of therapeutic intervention (Chamuleau et al., 2002). A third study was based on CABG being performed in patients with an FFR < 0.75 but not in patients with FFR ≥ 0.75. However, PTCA was used in the latter group if there were other stenoses present that were suitable for this intervention (Bech et al., 2001b). The results from these studies are summarised in Table 12. These studies are detailed further in Appendix G.

Table 12 Summary of non-randomised studies with an intervention determined by FFR level

Reference	Intervention	All cause mortality		MI		MACE	
		intervention		intervention		intervention	
		Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)
(Bech et al., 2001b)	CABG v no CABG	3	0			17	24
(Botman et al., 2004)	CABG V PCI	2.3	0	4.6	3.2	18.4	19.1
(Jasti et al., 2004)	PCI/CABG v nil	0	8.1			0	10
(Jimenez-Navarro et al., 2004)	Revascularisation v nil	29	10				
(Lopez-Palop et al., 2004)	Revascularisation v nil	Not stated	5	14	0*		
(Reczuch et al., 2004)	PCI v nil					13	8**
(Rieber et al., 2002b)	PCI v nil	12.5	0***			42	11****

*$P < 0.05$
**Coronary revascularisation
***$P = 0.01$
****$P = 0.001$

The study population was restricted to patients who were SPECT test negative in the study by Chamuleau et al (2002). Given the difference in event rates between the group of patients with FFR ≥ 0.75 and the group of patients with FFR < 0.75, additional useful information was obtained by measuring FFR in this SPECT negative group, since the study population was restricted to SPECT negative patients. However, it was not possible to determine whether a proportion of patients with FFR ≥ 0.75 were SPECT positive. Therefore, it was not possible to determine the comparative performance of FFR and SPECT.

Rieber et al (2002b) restricted their study population to patients with negative, inconclusive or missing stress test results. Twenty-three of the 48 participants with FFR < 0.75 had either non-pathologic or non-diagnostic stress test results, indicating that the measurement of FFR provided useful data in these 23 patients. However, it was not possible to determine the overall comparative performance of FFR and stress testing since stress testing was not conducted in all study participants.

These studies were characterised by variable lengths of follow-up, ranging from 12 to 38 months, and variable sample sizes, ranging from 16 to 150 (median 58). Four statistically significant differences were found, all with higher proportions of adverse outcomes in the intervention group. In the study by Lopez-Palop et al (2004), the proportion having an MI in the one year of follow-up was 14 per cent in the group with an FFR < 0.75 compared with 0 per cent in the group with an FFR ≥ 0.75 ($P = 0.04$). Chamuleau et al (2002) found a significant difference in the proportion with a cardiac event between the group with FFR ≥ 0.75 and the group with FFR < 0.75 (8.7% versus 26.7% respectively, $P = 0.04$). There was no form of intervention used in this study, irrespective of FFR level. If it is assumed that FFR would normally only be measured to consider a change in management, then this study provides little useful information in relation to the impact of FFR measurement on health outcome. The two other significant differences were found in the study by Rieber et al (2002b). In this one-year follow-up study, all cause mortality was higher in the group with an FFR < 0.75 compared with the group with an FFR ≥ 0.75 (12.5% versus 0%, $P = 0.01$). Event-free survival at 12 months was higher in

the group with an FFR ≥ 0.75 compared with the FFR < 0.75 group (89% versus 58%, $P = 0.001$).

Caution needs to be applied in interpreting the results of these studies due to:

- high potential for confounding, given they are not randomised controlled trials;
- the lack of a direct comparison between intervening and not intervening in the group with an FFR ≥ 0.75;
- variability in quality characteristics of the studies, which are detailed in Appendix G.

Non-randomised studies following patients with a restricted range of FFR results

This group of studies was characterised by being restricted to following patients with an FFR level greater than 0.75. The participants did not receive any form of coronary artery revascularisation. This group of studies should therefore be considered as uncontrolled studies, although they do provide some information about the level of adverse outcomes in patients with stenoses that were considered functionally non-significant. One of these studies focussed on a different research question to the question of interest in this review. In this study patients were stratified on the basis of their C reactive protein (CRP) level, in order to investigate whether CRP provided prognostic information in patients with an FFR ≥ 0.75 (Meuwissen et al., 2003). There were four studies in this group and the study results are summarised in Table 13.

Table 13 Summary of non-randomised studies following patients with FFR ≥ 0.75

Reference	n	Duration of follow-up	Mortality (%)	MI (%)	Revascularisation (%)	MACE (%)
Bech 1998	100	Mean 18 months	3**			22
Garcia 2001	43	Mean 11 months	0	0	12	
Meuwissen 2003	71	Mean 318 days	0*	0	8	
Ozdemir 2002	51	Mean 17 months	0	0	6	

*Cardiac mortality only
**KM survival (42 months): 97%

Meuwissen et al (2003), restricted their study population to patients with non-conclusive stress test results, therefore the measurement of FFR provided some clarification of functional status in these patients. Bech et al (1998) performed stress tests in 64 of the 100 participants. Twenty-eight of these were positive, indicating a discrepancy between the FFR level and the stress test result. However, only two of these 28 (7 per cent) patients had a coronary event.

These results suggest a low proportion of adverse events in the group who did not have any form of coronary intervention due to an FFR ≥ 0.75. However, the lack of a comparison group means it is not possible to estimate the event rate that would have occurred had an intervention, such as PTCA, been performed in these patients. Therefore, at best these studies provide supporting evidence that deferral of an intervention based on a high FFR is associated with a low proportion of events in the context of a population with intermediate coronary artery stenoses.

Subgroups of interest

Single lesion disease

The majority of studies included a study population with only a single stenosis suitable for PCI, though some had multiple stenoses. Most importantly, both RCTs were conducted in patients with a single stenosis (Bech et al., 2001a, Leesar et al., 2003). The study comparing FFR measurement to a reference standard of the "triple stress test" was also restricted to patients with single intermediate stenoses (Pijls et al., 1996). Other studies with either single lesion disease or single lesions that were amenable to PCI were also appraised (Jasti et al., 2004, Jimenez-Navarro et al., 2004, Lopez-Palop et al., 2004, Chamuleau et al., 2002, Rieber et al., 2002b, Bech et al., 2001b, Meuwissen et al., 2003, Hernandez Garcia et al., 2001, Bech et al., 1998).

The strongest evidence comes from the two RCTs. As documented above, one of these studies compared FFR measurement with stress testing. This study did not find any significant difference in outcome, but the study had low power since there were only 35 participants in each study arm. The other RCT did not find any overall difference in the proportion with a major adverse cardiac event among those with an FFR ≥ 0.75 who had PTCA deferred, compared with those who proceeded with PTCA. However, there was a significantly higher proportion of patients free from angina at 24 months in the defer group than in the perform group ($P = 0.02$).

The study comparing FFR level with the results of the "triple stress test" estimated FFR had a sensitivity of 87.5 per cent (95% CI 67.6-97.3) and specificity of 100 per cent (95% CI 83.9-97.3). However, caution needs to be applied when interpreting these results since the reference standard should be considered as imperfect.

There are also limitations to the remaining non-randomised studies and these studies add little to the findings of the RCTs. However, their findings are consistent with the RCT results.

Left main coronary artery disease

Three studies were identified that were restricted to study populations with left main CAD (Jasti et al., 2004, Jimenez-Navarro et al., 2004, Bech et al., 2001b).

Jasti et al (2004) studied patients with angiographically ambiguous left main CAD and patients were divided into two groups: FFR ≥ 0.75 and FFR < 0.75. The former received no intervention whereas the latter received either PCI or CABG. There was no significant difference in event-free survival between the two groups.

Jimenez-Navarro et al (2004) used a similar study design, with no intervention being offered to those with FFR ≥ 0.75 and either PCI or CABG being performed in the FFR < 0.75 group. There was no statistically significant difference between the two patient groups in all cause mortality or cardiac mortality in this small study.

The third study was based on CABG being performed in patients with an FFR < 0.75 but not in patients with FFR ≥ 0.75. However, PTCA was used in the latter group if there were other stenoses present that were suitable for this intervention (Bech et al., 2001b). The study results are presented in Table 14.

Table 14 Comparison of outcome in patients with left main CAD in a study where CABG operation was determined by FFR level

Outcome	FFR ≥ 0.75, No CABG[1]	FFR < 0.75, CABG performed
Three-year survival	100%	97%
Cardiac event-free survival	76%	83%
Mean CCS angina class		
Baseline	2.8	3.4
Last follow-up	1.6	1.5
Statistical significance (last follow-up compared with baseline)	*P* < 0.001	*P* < 0.001

[1] PTCA used if suitable lesions were present in this group

These three studies were all non-randomised. The only statistically significant finding was an improvement in angina status from before to after FFR measurement (regardless of intervention status). Caution needs to be applied in interpreting the results presented in this section since it is not possible to estimate the event rate that would have occurred had an intervention been offered to the group that had the intervention deferred.

Multiple lesion disease

Three studies were identified as consisting of a population with multiple, intermediate stenoses (Botman et al., 2004, Reczuch et al., 2004, Ozdemir et al., 2002). Two had multi-vessel disease (Botman et al., 2004, Reczuch et al., 2004). One of the three studies was restricted to patients with an FFR ≥ 0.75 (Ozdemir et al., 2002). One other study included a group of patients with multiple lesions but this study only examined the measurement of FFR in patients who had received PTCA and/or stenting (Pijls et al., 2002b).

Botman et al (2004) divided their study population into two groups:

1. Three arteries with significant stenosis (FFR ≤ 0.75) or two arteries including the proximal LAD: CABG performed.

2. All other patients received PCI.

The first group had 87 participants and the second group 63 participants. There was no significant difference between the two groups in all cause mortality, MI, angina, CABG, PTCA or major adverse cardiac event rates.

In a study of 16 participants Reczuch et al (2004) included eight patients with an FFR > 0.75 who had no intervention and another eight patients with FFR > 0.75 who received PCI. There was no significant difference in the proportion that subsequently required revascularisation over a mean follow-up period of 15 months.

The study restricted to 51 participants with an FFR ≥ 0.75 had a low event rate (Ozdemir et al., 2002). There were no deaths or MIs over a mean follow-up of 16 months and 6 per cent had a target-vessel revascularisation.

Overall, there were limited data relating to the effectiveness of FFR measurement in patients with multiple intermediate stenoses and there were limitations to the design of studies included in this section. While there were no significant differences in outcome

between groups with different FFR levels and, therefore, different interventions, one study in particular had a small sample size. It is also not possible to estimate the event rate that would have occurred had an intervention been offered to the group that had the intervention deferred.

Myocardial infarction and unstable angina

The RCT comparing FFR measurement with stress testing consisted of a study population with unstable angina or non-ST segment elevation MI (Leesar et al., 2003). There was insufficient information to disentangle outcome data within these two population groups. This study did not find any significant difference in outcome but had low power since each study arm had only 35 participants.

No studies were identified that provided data on the effectiveness of FFR measurement in population groups restricted to those with unstable angina or recent MI.

Other subgroups

Other subgroups of interest included:

- diffuse lesions
- transplant vasculopathy
- left ventricular dysfunction
- left ventricular hypertrophy
- microvascular disease
- diabetes
- hypertension

While the studies selected included patients relevant to most of these subgroups, there was insufficient information presented in the specific studies to disentangle outcomes related to FFR measurement within these subgroups. For example, many studies presented data on the proportion of participants with specific risk factors for CAD, including diabetes and hypertension, but did not document outcome by risk factor. The studies selected would also suffer from lack of power to present meaningful outcome data within such subgroup analyses. A potentially important subgroup where measuring FFR may have a distinct advantage over stress testing would be patients with either diffuse lesions or multiple lesions in the same vessel. However, while measuring FFR across multiple lesions in the same vessel may identify the lesion that is haemodynamically significant, there were no studies identified that demonstrated an improved outcome among patients receiving the FFR-guided approach compared with the stress test-guided approach.

Summary of results for the measurement of FFR in patients with an intermediate lesion on coronary angiography

A range of study designs was used in the 15 studies identified as being relevant to the effectiveness of measuring FFR in patients with an intermediate lesion on coronary angiography. No studies were identified in relation to the use of CFR in this section.

Study designs were divided into two RCTs, one study comparing FFR with the "triple stress test" as the reference standard, eight non-randomised studies following patients with a range of FFR levels, and four non-randomised studies following patients with an FFR that was considered to be functionally non-significant.

One RCT compared a stress test strategy with an FFR measurement strategy and did not find any significant difference in outcome between the two strategies. However, this study had a small sample size (n = 35 in each study arm). The other RCT randomised the group of patients with FFR ≥ 0.75 to either receive (perform group) or not receive (defer group) PTCA. The participants with FFR < 0.75 all received PTCA. There was a significantly higher proportion of patients free from angina at 24 months in the defer group than the perform group ($P = 0.02$), although there was no overall difference in event-free survival between these two groups. However, there was a significant difference in the event-free survival between the defer group and the group with an FFR < 0.75 (defer group: 89% versus group with FFR < 0.75: 78%, $P = 0.03$). This latter study provided the most reliable data but it did not compare FFR measurement with stress testing and had a narrow study population.

One study was identified that allowed a comparison between FFR and the "triple stress test" (Pijls et al., 1996). The sensitivity and specificity of FFR in comparison with the reference standard of the "triple stress test" were 87.5 per cent (95% CI 67.6-97.3) and 100 per cent (95% CI 83.9-97.3) respectively. However, caution needs to be applied in interpreting the results of this study since the reference standard is unlikely to be of perfect sensitivity and specificity.

In the majority of the third group of studies, patients with an FFR < 0.75 proceeded with the planned intervention whereas patients with an FFR ≥ 0.75 usually had the intervention deferred. While the studies with statistically significant results all had lower event rates among the group where intervention was deferred, caution needs to be applied in interpreting these results. This is because it is not possible to estimate the event rate that would have occurred had an intervention been offered to the group who had the intervention deferred. Some lower level evidence (Level III-2 evidence) supported additional benefit being obtained from FFR testing compared with stress testing, where the results of stress testing were either negative or equivocal.

In the final group, studies were restricted to patients who had no intervention as a result of an FFR ≥ 0.75. Little can be concluded from these uncontrolled studies, although the event rates were consistent with event rates in the groups where intervention was deferred in the other study designs.

Various subgroups of interest were investigated. The majority of studies included a study population with only a single stenosis suitable for PCI, though patients had either a single stenosis or multiple stenoses. It was identified that measuring FFR across multiple lesions in the same vessel may identify the lesion that is haemodynamically significant, which would not be possible with stress imaging. However, no studies were identified that demonstrated an improved outcome among patients receiving the FFR-guided approach compared with the stress test-guided approach.

The overall conclusion from the effectiveness studies for indication 1 is that using coronary pressure wires to measure FFR to assess intermediate coronary stenoses appears to have similar diagnostic accuracy compared with stress imaging. It also appears

to be safe to defer coronary intervention if the FFR is ≥0.75. However, there currently exists no evidence of different patient outcomes resulting from a difference in pre-coronary revascularisation procedure decisions with regards to whether or not a stress test or FFR measurement is performed.

Indication 2: Measurement of FFR in patients who have received PTCA and/or stenting

There were four studies identified that were relevant to this review indication. Important differences existed between the study designs. Firstly, there was variation in the cut point used to categorise functionally important and non-important FFR levels post intervention. The levels varied between 0.90 and 0.94. There was also variation in whether any form of management was changed as a result of the FFR level. All studies were non-randomised. Study details are provided in Appendix G.

Muramatsu et al 2002

This study used a cohort design with the 155 participants divided into three groups (Muramatsu et al., 2002):

1. FFR ≥ 0.94: No further treatment given.
2. FFR < 0.94: Stent inserted.
3. Directly stented without measuring FFR.

There was no significant difference in survival at 700 days between the group with FFR measured (90%) and the group directly stented (89%).

There were important limitations to this study:

- There were baseline differences between the study groups so confounding is likely to be present. For example, 80 per cent of the FFR group received a multilink stent compared with 68 per cent of the group who were directly stented.
- Non-consecutive patients were used.
- The study had low power to detect a difference in survival and no other outcome measures were presented.

Pijls et al 2002

This registry-based study was conducted in five centres in the United States, five centres in Europe and five centres in Asia (Pijls et al., 2002b). The 744 participants were categorised by FFR level following stent insertion. There was no change in management resulting from the FFR measurement. For example, further steps to improve FFR measurement among those with an initially low FFR were not attempted. The univariate study results are summarised in Table 15. Multivariate analysis identified two independent predictors of outcome: FFR category ($P < 0.001$) and length of stent ($P < 0.01$).

Table 15 Proportion with an event, by FFR level post stenting in a multicentre registry-based study

FFR level post stenting	Proportion with an event* (%)
0.75-0.80	29.5
0.81-0.85	22.2
0.86-0.90	16.2
0.91-0.95	6.2
0.96-1.00	4.9

*Mortality, MI or coronary revascularisation

While this study identified that low FFR levels were associated with increased risk of a subsequent event, it could not be established whether a change in management would reduce the event rate among those with a low FFR. Important quality characteristics of the study included:

- a high follow-up rate (99.2% at six months);
- FFR could not be measured in five patients post stenting (0.7%);
- blinding status not stated;
- information on age range and gender not documented, limiting knowledge about the spectrum of patients.

Rieber et al 2002

This registry-based study followed 89 participants for a mean of 10.9 months (Rieber et al., 2002a). The study compared the outcome in patients with an FFR > 0.94 with those who had an FFR < 0.94 following elective stent implantation. Sixteen events occurred, including cardiac mortality in 6 per cent, MI in 1 per cent and coronary revascularisation in 11 per cent. Multivariate analysis found FFR was significantly associated with outcome with a risk ratio of an adverse outcome in the group with FFR < 0.94 compared with FFR > 0.94 of 3.50 (95% CI 1.29-9.52).

As with the previous study, while this study identified that low FFR levels were associated with increased risk of a subsequent event, it could not be established whether a change in management would reduce the event rate amongst those with a low FFR. Characteristics of this study included:

- 100 per cent follow-up;
- blinding status was not stated;
- information on age range was not documented, limiting knowledge about the spectrum of patients;
- consecutive sampling was used;
- potential for confounding. For example, confounding by type of stent.

Bech et al 1999

This registry-based study reported on outcome after 24 months follow-up in a group of 58 participants (Bech et al., 1999). The study examined outcome based on an adequate functional result (defined as FFR ≥ 0.90) and an adequate anatomic result (diameter stenosis on angiography < 35%). No intervention was used in patients with an inadequate result. Events considered were mortality, MI, unstable angina and coronary artery revascularisation. The event-free survival at 24 months with both optimal anatomic and functional results was significantly higher than with a suboptimal result (88% versus 59%, $P = 0.01$). The authors stated "an almost similar event-free survival was observed" when FFR was used alone. On multivariate analysis, FFR was associated with risk of an adverse event ($P < 0.01$).

While this study also identified that low FFR levels were associated with increased risk of a subsequent event, it could not be established whether a change in management would reduce the event rate among those with a low FFR. This study was restricted to patients who did not receive a stent.

Characteristics of this study included:

- 100 per cent follow up at 24 months;
- 58 of 60 (97%) of the eligible population participated and the other two proceeded straight to CABG when PTCA was unsuccessful;
- blinding status not stated;
- information on age range not documented, limiting knowledge about the spectrum of patients;
- potential for confounding given the study design used.

Subgroups of interest

One study was restricted to patients with recent MI (Muramatsu et al., 2002). There was no overall difference in survival at 700 days between a group of 77 participants with FFR measured and a group of 78 participants who were directly stented without FFR measurement.

It was not possible to disentangle outcome data for the other subgroups of interest in relation to the use of FFR following PTCA with or without stenting.

Summary

Four studies were identified examining the effectiveness of FFR measurement following intervention (whether it was PTCA alone or in conjunction with a coronary stent). One study compared FFR measurement with a strategy of directly stenting patients. There was no significant difference in survival between these two groups, but the study had low power to detect any difference in survival. The other three studies compared patient outcome by FFR level. While low FFR levels were associated with adverse outcome, it was not possible to interpret if a change in management would improve health outcome among those with low FFR levels. This limitation was due to the lack of change in management within the study designs.

What are the economic considerations?

Introduction

The purpose of this economic appraisal is to evaluate the value for money of the measurement of FFR for two indications: (1) in order to guide the decision of whether to proceed with PCI (PTCA alone or with stenting) in patients with intermediate lesions; and (2) in order to evaluate the effectiveness of a PCI procedure. Decision analysis is used to estimate the incremental health care costs of this technique over those of the comparators: delaying the decision for PCI until the result of a nuclear stress test can be observed; and, performing PCI on all intermediate lesions.

The specific objectives for the economic analysis were to:

- identify and review recent published studies reporting economic evaluations of the relevant strategies;
- identify what approach should be used in the economic evaluation (ie cost-minimisation, cost-effectiveness, cost-utility, or cost-benefit);
- identify the test result probabilities, treatment probabilities, and cost-estimate parameters, and the appropriate modelling device for outcome analysis;
- identify the quantifiable benefits of FFR measurement over the comparators;
- identify the cost differences between FFR measurement and the comparators;
- evaluate the robustness of the results by sensitivity analysis.

FFR measurement in patients with an intermediate lesion on coronary angiography

Because measurement of FFR can be performed in the cardiac catheter laboratory immediately prior to PCI, the major benefit of measuring FFR over nuclear stress testing appears to be that the results will reliably indicate which patients may have PCI safely deferred without splitting the angiography and PCI procedures, and without introducing a delay in the decision to proceed or not with PCI. The economic analysis focused, therefore, on determining whether the cost of identifying patients in whom PCI may be safely deferred is reduced when patients are kept in the cardiac catheter laboratory for FFR measurement rather than sent out of the laboratory for nuclear stress testing and potentially returning later for PCI. All costs are considered to determine whether there is an expected reduction in net costs.

The major benefit of measuring FFR in order to guide the decision of whether to proceed with PCI rather than performing PCI on all intermediate lesions appears to be that FFR measurement may safely identify a proportion of patients for whom PCI can be safely deferred, eliminating the cost and unpleasantness of unnecessary surgery while saving the costs associated with splitting the initial angiography and angioplasty.

To establish the cost differential between FFR measurement with a coronary pressure wire and the comparators, it is necessary to determine not only the costs directly and indirectly associated with the tests and with PCI, but also to include flow-on costs such as variations in management costs. To determine the significance of any cost differential, these costs need to be balanced against any expected change in patient outcomes that is associated with the decision to defer or not to defer PCI.

The conclusion of the effectiveness section is that there currently exists no evidence of different patient outcomes resulting from a difference in pre-coronary revascularisation procedure decisions with regards to whether or not a stress test or FFR measurement is performed. Therefore, cost-minimisation analysis was selected as the most appropriate evaluation technique for this review. In the absence of relevant clinical trials providing Australian cost data, costs have been derived from literature-based estimates, existing data and expert opinion.

Relevant economic literature

Two published studies were identified that presented the economic aspects of the intervention and the comparators, which met the inclusion criteria for the review.

Fearon et al. (2003) included a full economic analysis of the cost-effectiveness of FFR measurement in patients with intermediate lesions. Three strategies were considered: (1) deferring the decision to perform PCI in order to perform a nuclear stress test; (2) measuring FFR at the time of angiography in order to guide the decision for PCI; and (3) stenting all intermediate lesions. This study was based on American cost data, so its results may not be applicable to the Australian context. The study did, however, indicate that there is a significant additional cost associated with splitting the angiography and the PCI in order to perform a nuclear stress test, and that this cost would not be incurred if a coronary pressure wire was used to measure FFR in the cardiac catheter laboratory. The results suggested that the FFR strategy saved US$1,795 per patient relative to the nuclear stress test strategy and US$3,830 relative to the strategy of stenting all intermediate lesions.

Leesar et al. (2003) compared FFR measurement with stress perfusion scintigraphy (SPS) and concluded similarly that the use of FFR reduces the duration and cost of hospitalisation compared with SPS. Specifically, patients undergoing SPS were transferred back to a monitored bed following angiography and underwent SPS the next day whereas patients undergoing FFR measurement had the procedure immediately following cardiac catheterisation. Overall, patients undergoing SPS spent approximately 49 hours in hospital compared with 11 hours for patients undergoing FFR measurement.

Every effort was made in this review to capture the economic implications of this effect subject to the limitations of Australian cost data, given the strong suggestion in the literature that the pivotal factor in the cost differential between FFR measurement and stress testing is likely to be related to the additional costs incurred when the initial angiography is split from a subsequent PCI procedure.

Decision model

Assumptions of the model

There would be approximately 8,862 patients annually, based on 88,618 coronary angiographies performed in Australia annually (total number for 2002-03, Australian Institute of Health & Welfare (AIHW), 2004), and approximately 10 per cent (15% is used for sensitivity analysis) of these revealing intermediate coronary lesions, based on the expert opinion of the MSAC Advisory Panel. The decision model, shown in Figure 4, starts in the cardiac catheter laboratory at the time of initial angiography, where one of three strategies is followed for treating a patient with an intermediate lesion:

1- The patient proceeds directly to PCI.

- A- In 95 per cent of these cases (according to the expert opinion of the MSAC Advisory Panel), PCI will involve angioplasty and stenting.
- B- In five per cent of these cases (according to the expert opinion of the MSAC Advisory Panel), PCI will involve angioplasty only.

2- The patient will undergo nuclear stress testing.

- A- In approximately 44 per cent of cases (Leesar et al., 2003), the test produces ischemia (According to the expert opinion of the MSAC Advisory Panel, nuclear stress testing would be expected to produce the same proportion of patients with ischemia as FFR measurement, on which Bech et al. is based. This variable is tested in the sensitivity analysis). Consequently, the patient will be readmitted for PCI.
  - i- In 95 per cent of these cases (according to the expert opinion of the MSAC Advisory Panel), PCI will involve angioplasty and stenting.
  - ii- In 5 per cent of these cases (according to the expert opinion of the MSAC Advisory Panel), PCI will involve angioplasty only.
- B- In approximately 56 per cent of cases (Leesar et al., 2003), the test does not produce ischemia. Consequently, the PCI is deferred.

3- The patient will undergo FFR measurement.

- A- In approximately 44 per cent of cases (Bech et al., 2001a), the FFR measurement is under 0.75. Consequently, the patient will proceed to PCI.
  - i- In 95 per cent of these cases (according to the expert opinion of the MSAC Advisory Panel), PCI will involve angioplasty and stenting.
  - ii- In 5 per cent of these cases (according to the expert opinion of the MSAC Advisory Panel), PCI will involve angioplasty only.
- B- In approximately 56 per cent of cases (Bech et al., 2001a), the FFR measurement is 0.75 or greater. Consequently, the PCI is deferred.

Direct to PCI strategy

Where patients are expected to proceed directly to PCI following initial angiography, the procedures take place within the cardiac catheter laboratory. If the procedures are carried out by a single operator, the relevant Medicare item numbers are:

- 59925 for angiography;
- 38246 for placement of catheters; and either
- 35304 for angioplasty without stenting; or
- 35310 for stenting.

If the procedures are carried out by different operators (this would be the case in approximately 20 per cent of cases according to the expert opinion of the MSAC Advisory Panel), the relevant Medicare item numbers are:

- 59925 for angiography (first operator);
- 38218 for placement of catheters (first operator);
- 59912 for angiography (second operator);
- 38243 for placement of catheters (second operator); and either
- 35304 for angioplasty without stenting (second operator); or
- 35310 for stenting (second operator).

Other cost data are derived from the National Hospital Cost Data Collection:

- AR-DRG F15Z, for the cost of angioplasty with stenting. Because patients proceeding directly to PCI are having coronary angiography as part of the same procedure as the PCI procedure, the AR-DRG cost is assumed to include costs associated with angiography that are not covered by Medicare fees.
- AR-DRG F16Z, for the cost of angioplasty without stenting. Because patients proceeding directly to PCI are having coronary angiography as part of the same procedure as the PCI procedure, the AR-DRG cost is assumed to include costs associated with angiography that are not covered by Medicare fees.

Stress testing strategy

Where patients will undergo a stress test following initial angiography, the test is typically a stress thallium or stress echo test (expert opinion of the MSAC Advisory Panel). These patients are generally discharged following the initial angiography and return on an outpatient basis for the stress test. The results of the stress test would be reviewed with the specialist on another occasion. If the decision is not to proceed with PCI, which is

usually if the stress test does not produce ischemia, the patient receives appropriate pharmacological treatment.

If the decision is to proceed to PCI, which is usually if the stress tests produces ischemia, the patient is admitted to hospital for the PCI and will need to undergo a second angiography at that time. The relevant Medicare item numbers are:

- 59925 for angiography;
- 38218 for placement of catheters;
- 61307 for combined stress and rest myocardial perfusion study;
- 11712 for ECG monitoring and recording; and
- 116 for a consultation to review results.

For coronary angiography that is performed without proceeding immediately to PCI, as is the case with all initial angiography for patients undergoing stress testing, the cost components of the angiography that are not covered by Medicare fees are assumed to be $1,215 in public hospitals and $2,500 in private hospitals (expert opinion of the MSAC Advisory Panel).

If the patient is re-admitted for PCI, the additional relevant Medicare numbers are:

- 59912 for angiography;
- 38246 for placement of catheters; and either
- 35304 for angioplasty without stenting; or
- 35310 for stenting.

Other cost data is derived from the National Hospital Cost Data Collection:

- AR-DRG F15Z for the cost of angioplasty with stenting
- AR-DRG F16Z for the cost of angioplasty without stenting

FFR measurement strategy

There currently exists no MBS item for FFR measurement. The direct cost of FFR measurement includes two components: the cost of consumable equipment and the labour cost. The consumable equipment cost associated with FFR measurement is $1,250 for the pressure wire (cost provided by the applicant). According to the expert opinion of the MSAC Advisory Panel, the labour cost associated with FFR measurement would be approximately $250. In addition, where FFR measurement results in the patient proceeding to PCI, the use of the pressure wire would remove the need for the standard

guidewire, the cost of which is approximately $140 (expert opinion of the MSAC Advisory Panel).

As shown in Table 16 below, the additional direct cost of FFR measurement is, therefore, estimated to be $1,500 when FFR measurement does not lead to PCI and $1,360 when FFR measurement leads to PCI.

Table 16 Total direct cost of FFR measurement

Result of FFR measurement	Cost component	Cost
FFR >= 0.75	Consumable equipment	$1,250
PCI deferred	Labour	$250
	Total direct cost	**$1,500**
FFR < 0.75	Standard guidewire (replaced by pressure wire)	-140
Patient proceeds to PCI	**Total direct cost**	**$1,360**

FFR measurement takes place in the cardiac catheter laboratory at the time of initial angiography. If the FFR is 0.75 or higher, the PCI is generally deferred and the patient receives appropriate pharmacological treatment. If the FFR is below 0.75, the patient generally proceeds to PCI and the procedure takes place immediately. Unlike stress testing, therefore, FFR measurement does not require an additional angiography, repeated placement of catheters, or a consultation with a specialist for patients who proceed to PCI. If the procedures do not result in the patient proceeding to PCI, the relevant Medicare item numbers are:

- 59925 for angiography; and
- 38218 for placement of catheters.

If the procedures are carried out by a single operator and these result in the patient proceeding to PCI, the relevant Medicare item numbers are:

- 59925 for angiography;
- 38246 for placement of catheters; and either
- 35304 for angioplasty without stenting; or
- 35310 for stenting.

If the procedures are carried out by different operators (this would be the case in approximately 20 per cent of cases according to the expert opinion of the MSAC Advisory Panel) and result in the patient proceeding to PCI, the relevant Medicare item numbers are:

- 59925 for angiography (first operator);
- 38218 for placement of catheters (first operator);

- 59912 for angiography (second operator);
- 38243 for placement of catheters (second operator); and either
- 35304 for angioplasty without stenting (second operator); or
- 35310 for stenting (second operator).

Other cost data is derived from the National Hospital Cost Data Collection:

- AR-DRG F15Z for the cost of angioplasty with stenting
- AR-DRG F16Z for the cost of angioplasty without stenting

Furthermore, for angiograms that are performed without proceeding to PCI within the same admission, the cost components of the angiography that are not covered by Medicare fees are assumed to be $1,215 in public hospitals and $2,500 in private hospitals (expert opinion of the MSAC Advisory Panel).

Pharmacological treatment

This analysis does not include the cost of pharmacological treatment, which typically includes lifelong aspirin and will also include clopidogrel where a patient has undergone PCI. Because the proportion of patients who undergo PCI is expected to be the same in the stress testing strategy and in the FFR measurement strategy, the total cost of drugs for these two strategies is expected to be the same. The direct to PCI strategy is expected to be associated with a higher drug cost due to the greater proportion of patients who undergo PCI. The existence of this additional cost should be considered along with the conclusions of the analysis.

Cost estimates

In addition to the description of the three strategies, provided above, the following assumptions were made in the economic analysis:

- Approximately 45 per cent of patients with intermediate lesions will be treated in public hospitals and approximately 55 per cent will be treated in private hospitals (based on the percentage of angiographies performed in public and private hospitals in 2002-03 according to the Australian Institute of Health & Welfare (AIHW), 2004).
- The AR-DRG cost per admission for angioplasty with stenting, $6,085 in public hospitals and $12,086 in private hospitals (National Hospital Cost Data Collection cost weights for version 4.2, round 7, 2002-03, item F15Z), accurately reflects the cost of an admission leading to angioplasty with stenting, which is assumed to be the case in 95 per cent of PCI procedures.
- The AR-DRG cost per admission for angioplasty without stenting, $4,983 in public hospitals and $8,254 in private hospitals (National Hospital Cost Data Collection cost weights for version 4.2, round 7, 2002-03, item F16Z), accurately reflects the cost of an admission leading to angioplasty without stenting, which is assumed to be the case in 5 per cent of PCI procedures.

- The Medicare Benefits Schedule reimbursement fees itemised in Table 21 below accurately reflect the direct costs of the relevant procedures.

- The total direct cost of FFR measurement where the patient does not proceed to PCI consists of two components, a consumables cost of $1,250 for the pressure wire (provided by the applicant) and a labour cost of approximately $250 (expert opinion – lower possible labour costs are considered in the sensitivity analysis);.

- If FFR measurement leads to PCI, the cost of the standard guidewire (approximately $140) is not incurred, as the pressure wire is used in its place.

- The cost of Adenosine, which is needed for FFR measurement, is insignificant (expert opinion of the MSAC Advisory Panel).

- The true cost of procedures varies according to whether procedures are performed alone, in combination with other procedures, or are performed by more than one operator. Therefore, it is assumed that the billing procedures under the Medicare reimbursement system accurately capture this effect, allowing for 100 per cent of the Medicare fee to capture the true cost of the most costly procedure, 50 per cent of the Medicare fee to capture the true cost of the next most costly procedure, and 25 per cent of the Medicare fee to capture the true cost of any other procedures, where angiography (item numbers 59925 and 59912) is exempted from this rule.

- Cost estimates are for a single lesion per patient.

The Medicare Benefits Schedule items used in this analysis are detailed in Table 17 below.

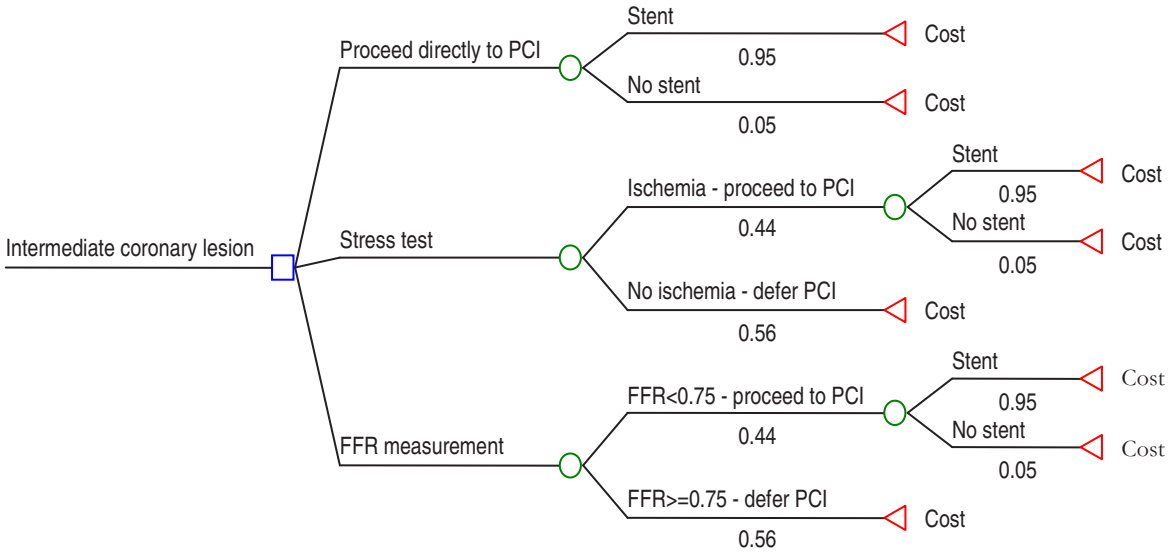
Table 17 Medicare Benefits Schedule items used in economic analysis

Item Number	Description	Fee
116	Each attendance (other than a service to which item 119 applies) subsequent to the first in a single course of treatment	$64.10
11712	Multi-channel ECG monitoring and recording during exercise (motorised treadmill or cycle ergometer capable of quantifying external workload in watts) or pharmacological stress, involving the continuous attendance of a medical practitioner for not less than 20 minutes, with resting ECG, and with or without continuous blood pressure monitoring and the recording of other parameters, on premises equipped with mechanical respirator and defibrillator	$129.05
35304	Transluminal balloon angioplasty of 1 coronary artery, percutaneous or by open exposure, excluding associated radiological services or preparation, and excluding aftercare.	$437.35
35310	Transluminal stent insertion including associated balloon dilatation for coronary artery, percutaneous or by open exposure, excluding associated radiological services and preparation, and excluding aftercare.	$646.90
38218	Selective coronary angiography, placement of catheters and injection of opaque material with right or left heart catheterisation or both, or aortography, not being a service associated with a service to which item 38215, 38220, 38222, 38225, 38228, 38231, 38234, 38237, 38240 or 38246 applies	$564.55

Table 17 Medicare Benefits Schedule items used in economic analysis (continued)

Item Number	Description	Fee
38246	Selective coronary angiography, placement of catheters and injection of opaque material with right or left heart catheterisation or both, or aortography followed by placement of catheters prior to any coronary interventional procedure, not being a service associated with a service to which item 38215, 38218, 38220, 38222, 38225, 38228, 38231, 38234, 38237, 38240 or 38243 applies	$941.00
59912	Selective coronary arteriography, including the services described in item 59970, 59974 or 61109, not being a service to which item 59903 or 59925 applies	$305.20
59925	Selective coronary arteriography and angiocardiography, including the services described in items 59903, 59912, 59970, 59974 or 61109	$362.45
DIN.6 61307	Combined stress and rest, stress and re-injection or rest and redistribution myocardial perfusion study, including delayed imaging or re-injection protocol on a subsequent occasion – with single photon emission tomography and with planar imaging when undertaken	$826.65

Figure 4 Decision model for patients with intermediate lesions



Total cost per patient and incremental cost per patient

The expected total cost per patient was highest, and significantly higher, for the strategy of proceeding directly to PCI in both public and private hospital settings. The stress testing strategy was also associated with a slightly higher expected total cost per patient than the FFR measurement strategy. The difference in cost between the direct-to-PCI strategy and the two alternative strategies was due to the significantly greater probability of the patient undergoing PCI, which is estimated to be more costly than either the stress test or FFR measurement. The difference in cost between the stress testing strategy and the FFR measurement strategy was due to the cost associated with angiography being greater for patients undergoing stress testing because of the need for a second angiogram when these patients proceed to PCI. Total and incremental cost per patient results are presented in Table 18 below.

Table 18 Total and incremental cost per patient in public and private hospitals and as a weighted average[1]

	FFR measurement	Stress test	Direct to PCI
Total cost per patient, public hospital	5,291	5,216	6,030
Incremental cost per patient ($, relative to the lowest cost strategy), public hospital	75		814
Total cost per patient, private hospital	9,337	10,304	13,085
Incremental cost per patient ($, relative to the lowest cost strategy), private hospital		967	5,281
Total cost per patient ($), weighted average[1]	7,516	8,014	9,910
Incremental cost per patient ($, relative to the lowest cost strategy), weighted average[1]		498	2,394

[1] Small discrepancies may occur in this table due to rounding off.

Cost-effectiveness

Measurement of FFR before deciding on PCI is estimated to be a less costly strategy than stress testing and a significantly less costly strategy than proceeding directly to PCI. Given that the overall conclusion on effectiveness was that patient outcomes are no worse if a strategy of measuring FFR prior to PCI is followed, then this strategy should be considered significantly more cost-effective than proceeding directly to PCI, and more cost-effective than stress testing.

Total annual cost

Based on a total of 88,618 coronary angiographies performed in Australia in 2002-03 (see Clinical Need section, page 6), of which approximately 10 per cent (15 per cent used in sensitivity analysis) involve intermediate lesions (expert opinion of the MSAC Advisory Panel), total annual costs are estimated for three scenarios, showing the cost implications

of having all of these procedures preceded by one of the decisions considered in this review: to proceed directly with the PCI procedure; to delay the procedure in order to perform a stress test; or to measure FFR in the cardiac catheter laboratory in order to inform the decision of whether to proceed with the PCI. The costs of procedures performed in public and private hospitals are factored into the estimates according to the proportion of patients expected to receive treatment in each sector (45 per cent through public hospitals, 55 per cent through private hospitals).

As shown in Table 19, the total annual cost to the Australian health system for proceeding directly to PCI is estimated to be $87,823,669 for the approximately 8,862 patients with intermediate lesions who would be considered for PCI annually.

Table 19 Total annual public and private costs for a strategy of proceeding directly to PCI for all patients[1]

	Public	Private	Total
Expected cost per patient ($)	6,030	13,085	
Proportion of patients	45%	55%	
Weighted average cost per patient ($)			9,910
Number of patients	3,988	4,874	8,862
Total annual cost ($)	24,046,638	63,777,031	87,823,669

[1] Small discrepancies may occur in this table due to rounding off.

As shown in Table 20, the total annual cost to the Australian health system is estimated to be $71,023,699 for stress testing the approximately 8,862 patients with intermediate lesions who would be considered for PCI annually and proceeding with PCI only in cases where the stress test produces ischemia.

Table 20 Total annual public and private costs for a strategy of stress testing all patients prior to PCI[1]

	Public	Private	Total
Expected cost per patient ($)	5,216	10,304	
Proportion of patients	45%	55%	
Weighted average cost per patient ($)			8,014
Number of patients	3,988	4,874	8,862
Total annual cost ($)	20,800,232	50,223,467	71,023,699

[1] Small discrepancies may occur in this table due to rounding off.

As shown in Table 21, the total annual cost to the Australian health system is estimated to be $66,610,620 for measuring FFR in the approximately 8,862 patients with intermediate lesions who would be considered for PCI annually and proceeding with PCI only in cases where the FFR is less than 0.75.

Table 21 Total annual public and private costs for a strategy of measuring FFR in all patients prior to PCI[1]

	Public	Private	Total
Expected cost per patient ($)	5,291	9,337	
Proportion of patients	45%	55%	
Weighted average cost per patient ($)			7,516
Number of patients	3,988	4,874	8,862
Total annual cost ($)	21,100,282	45,510,338	66,610,620

[1] Small discrepancies may occur in this table due to rounding off.

As shown in Table 22, the use of FFR measurement is expected to result in an annual saving of approximately $21,213,049 compared with proceeding directly to PCI, and an annual saving of approximately $4,413,080 compared with stress testing.

Table 22 Total annual public and private costs and incremental costs for a strategy of measuring FFR in all patients prior to PCI[3]

	Total annual cost ($)			Total annual savings associated with FFR ($)	
	FFR	Stress test	Direct to PCI	Savings relative to direct to PCI strategy[1]	Savings relative to stress testing[2]
Public	21,100,282	20,800,232	24,046,638	2,946,356	-300,050
Private	45,510,338	50,223,467	63,777,031	18,266,693	4,713,129
Total	66,610,620	71,023,699	87,823,669	21,213,049	4,413,080

[1] Savings associated with a strategy of measuring FFR in all patients prior to PCI relative to a strategy of proceeding directly to PCI in all patients.

[2] Savings associated with a strategy to measure FFR in all patients prior to PCI relative to a strategy of stress testing all patients prior to PCI.

[3] Small discrepancies may occur in this table due to rounding off.

Sensitivity analysis

The conclusion of the decision analysis, using base case estimates of probabilities and costs, is that the use of FFR measurement is expected to result in slightly lower costs than stress testing and significantly lower costs than a strategy of proceeding directly to PCI. The purpose of sensitivity analysis is to test whether the conclusion derived from base case results is sensitive to plausible variations in the assumptions of the model.

Key assumptions of the model are tested as follows:

- The model is adjusted to allow for 5 to 10 per cent of patients undergoing stress testing to be admitted to hospital for one night, either because of long distances between the patient's home and the hospital or because the patient is already an inpatient, having been admitted for assessment of chest pain with no objective evidence of ischaemia. In the latter case, the patient may be admitted to a monitored bed to await a stress myocardial perfusion study.

- The proportion of patients who go on to have ischemia after FFR measurement is varied from 44 per cent (the figure suggested by the Advisory Panel) to 35 per cent (20 per cent lower than the base case) and to 53 per cent (20 per cent higher than the base case).

- Lower labour costs of $100 and $175 ($250 was used in the base case) are considered for FFR measurement.

- The higher end of the range for the number of patients annually with intermediate lesions is considered. According to the expert opinion of the MSAC Advisory Panel, approximately 10 to 15 per cent of the 88,618 coronary angioplasty procedures performed in Australia in 2002-03 would involve patients with intermediate lesions (10 per cent was used in the base case).

For patients who may be admitted to hospital following an exercise ECG, it is assumed that the cost of the overnight stay is consistent with the cost per day derived from AR-DRG item F74Z, Chest Pain. The average total cost per admission for this item is $1,278 in the public sector and $1,338 in the private sector, for an average length of stay of 1.6 days and 2.11 days respectively.

The estimated cost of an overnight stay is, therefore, $799 in the public sector and $634 in the private sector. For patients who are admitted to hospital because of distance from home, half of this cost is assumed due to these patients not requiring the monitoring that those with chest pain would require. These costs are shown in Table 23 below.

Table 23 Cost per overnight stay in hospital for patients awaiting thallium stress tests[1]

	Public hospital	Private hospital	All hospitals[2]
AR-DRG F74Z, Chest Pain, average total cost per admission	$1,278	$1,338	
AR-DRGF74Z, Chest Pain, average length of stay	1.6 days	2.11 days	
Derived cost per day / per overnight stay for patients with atypical chest pain	$799	$634	$708
Derived cost per day / per overnight stay for patients facing long distance travel	$400	$317	$354

[1] Small discrepancies may occur in this table due to rounding off.

[2] Weighted average assuming 45 per cent in public hospitals and 55 percent in private hospitals.

Adding an overnight stay due to atypical chest pain for 5 per cent of patients undergoing stress testing, and an overnight stay due to distance travelled for another 5 per cent of patients undergoing stress testing, results in an increase in the expected cost per patient for the stress testing strategy of $53. This increase has the effect of increasing the expected cost differential between the stress testing strategy and the FFR measurement strategy to $551 per patient. The effects on expected cost per patient are shown in Table 24.

Table 24 Total and incremental cost per patient when 10 per cent of patients undergoing stress testing require an additional overnight stay in hospital[1]

	FFR measurement	Stress test	Direct to PCI
Expected total cost per patient, base case	$7,516	$8,014	$9,910
Incremental cost per patient ($, relative to the lowest cost strategy), base case		$498	$2,394
Expected total cost per patient when 10 per cent of patients undergoing stress testing require an overnight stay	$7,516	$8,067	$9,910
Incremental cost per patient ($, relative to the lowest cost strategy) when 10 per cent of patients undergoing stress testing require an overnight stay		$551	$2,394

[1] Small discrepancies may occur in this table due to rounding off.

Although a labour cost of $250 for FFR testing was assumed in the base case, this may be at the higher end of possible labour costs and, therefore, may underestimate the potential savings associated with FFR testing. The effects of labour costs of $100 and $175 are considered in Table 25 below.

Table 25 Total and incremental cost per patient when the labour cost associated with FFR measurement is lower.[1]

	FFR measurement	Stress test	Direct to PCI
Expected total cost per patient, base case (labour cost of $250 for FFR measurement)	$7,516	$8,014	$9,910
Incremental cost per patient ($, relative to the lowest cost strategy), base case		$498	$2,394
Expected total cost per patient when the labour cost for FFR is $175	$7,441	$8,014	$9,910
Incremental cost per patient ($, relative to the lowest cost strategy) when 10 per cent of patients undergoing stress testing require an overnight stay		$573	$2,469
Expected total cost per patient when the labour cost for FFR is $100	$7,366	$8,014	$9,910
Incremental cost per patient ($, relative to the lowest cost strategy) when 10 per cent of patients undergoing stress testing require an overnight stay		$648	$2,544

[1] Small discrepancies may occur in this table due to rounding off.

Increasing the number of patients annually has no effect on expected cost per patient, and therefore has no effect on cost-effectiveness. However, as shown in Table 26 below, increasing the number of patients annually from 8,862 (10 per cent of the number of coronary angioplasty procedures in 2002-03) to 13,293 (15 per cent of the number of coronary angioplasty procedures in 2002-03) increases the potential annual savings generated by a strategy to measure FFR in all patients prior to PCI relative to a strategy of proceeding directly to PCI and relative to the stress testing strategy.

Table 26 Total annual public and private costs and incremental costs for a strategy of measuring FFR in all patients prior to PCI[3], assuming there are 13,293 patients annually

	Total annual cost ($)			Total annual saving associated with FFR ($)	
	FFR	Stress test	Direct to PCI	Savings relative to Direct to PCI strategy[1]	Savings relative to stress testing[2]
Base case (8,862 patients annually)					
Public	21,100,282	20,800,232	24,046,638	2,946,356	-300,050
Private	45,510,338	50,223,467	63,777,031	18,266,693	4,713,129
Total	66,610,620	71,023,699	87,823,669	21,213,049	4,413,080
With 13,293 patients annually					
Public	31,650,423	31,200,349	36,069,957	4,419,534	-450,074
Private	68,265,506	75,335,201	95,665,546	27,400,040	7,069,694
Total	99,915,929	106,535,549	131,735,503	31,819,574	6,619,620

[1] Savings associated with a strategy of measuring FFR in all patients prior to PCI relative to a strategy of proceeding directly to PCI in all patients.

[2] Incremental cost of a strategy to measure FFR in all patients over the cost of stress testing all patients prior to PCI.

[3] Small discrepancies may occur in this table due to rounding off.

FFR measurement in patients who have received PCI

Due to a lack of evidence regarding the effectiveness of the FFR measurement in evaluating the effectiveness of PCI, a full economic analysis was not undertaken for this indication. This section provides only a basic costing of the use of FFR measurement in evaluating the effectiveness of PCI: Only incremental direct costs are included. For the purpose of this analysis, it is assumed that FFR measurement would take place immediately following a PCI procedure and, therefore, not requiring additional angiography or other procedures.

The direct cost of FFR measurement is made up of two components: the labour cost, which would be approximately $250 (expert opinion of the MSAC Advisory Panel) and the cost of consumable equipment used for the FFR measurement, ($1,250 for the pressure wire).

For patients with intermediate coronary stenoses, the coronary pressure wire would have been used prior to PCI for FFR measurement. The same wire can then be used after PCI to assess the likelihood of restenosis. For these patients, the incremental direct cost per patient of performing FFR measurement following PCI is, therefore, approximately $250.

For patients with severe coronary stenoses, the use of coronary pressure wire to assess the likelihood of restenosis following PCI would be the first use of coronary pressure wire as these patients typically would not have FFR measurement prior to PCI. However, the use of coronary pressure wire would replace the use of a standard guidewire, the cost of which is assumed to be approximately $140 (expert opinion of the MSAC Advisory Panel). For such patients, the direct incremental cost per patient would, therefore, be approximate $1,360.

Conclusions

Safety

Twenty six studies involving 2639 participants were identified that met the eligibility criteria for the safety component of the review. These studies were selected on the basis of FFR and/or CFR being measured and safety concerns were related to the use of vasodilating agents to achieve maximal hyperemia and to the instrumentation required to measure FFR and CFR. The great majority of adverse effects reported were self limiting in nature. There was one episode of severe bronchospasm reported but no further information was reported on the management of this patient. The bronchospasm was thought to be due to the use of IV adenosine. Two type B coronary dissections were also reported, but these adverse events did not require any specific intervention. Therefore, the measurement of FFR was associated with a satisfactory safety profile.

Effectiveness

Indication 1: Measurement of FFR and CFR in patients with an intermediate lesion on coronary angiography

The studies identified for the evaluation of the effectiveness of FFR and CFR measurement in patients with intermediate coronary stenoses were of variable quality. Study designs ranged from RCTs through to uncontrolled studies. Two RCTs were identified. One compared stress testing to FFR measurement and the other compared intervening with not intervening in a group with FFR ≥ 0.75. The former RCT did not find any difference in outcome between stress test measurement and FFR measurement, but the study was underpowered with only 35 participants in each arm. In the other RCT there was a significantly higher proportion of participants free from angina at 24 months, although there was no overall difference in cardiac event rate, in the group where the intervention was deferred because the coronary pressure wire suggested the lesion was not haemodynamically significant. This study was restricted to participants with a single stenosis.

One study compared FFR measurement with a reference standard consisting of a "triple stress test". FFR had a sensitivity of 87.5 per cent (95% CI 67.6-97.3) and specificity of 100 per cent (95% CI 83.9-100) in that study. However, the reference standard should be considered as imperfect since it is unlikely to be 100 per cent sensitive and specific. Therefore, the true sensitivity and specificity of FFR is unclear from this study. Other studies also evaluated the diagnostic accuracy of FFR but these relied on a reference standard that consisted of a single stress test. The *a priori* selection criteria developed for this review excluded these studies from appraisal. Studies of diagnostic accuracy were limited to using the "triple stress test" as the reference standard because it was thought other tests would be inadequate for this purpose.

A third group of eight non-randomised studies followed patients for variable follow-up times. The eligibility criteria varied between studies and included study populations with differing characteristics, such as single versus multiple stenoses and acute MI versus non-

acute conditions. In most of these studies an intervention was offered to patients with an FFR < 0.75 but not to patients with an FFR ≥ 0.75. Where a statistically significant difference in outcome was identified, the proportion with an adverse outcome was higher in the group with FFR < 0.75. This type of study supports a lower risk of adverse outcome amongst participants with a high FFR, implying a functionally non-significant stenosis, but it is not possible to determine whether an intervention in the group with a high FFR would have reduced the event rate further.

A fourth group of four studies followed patients with an FFR ≥ 0.75. The proportion with an adverse event was similar to those with a high FFR in the previous category of studies. However, these studies were uncontrolled so do not allow any conclusions to be drawn on the effectiveness of FFR measurement in improving patient outcome.

Various subgroups of interest were investigated. The majority of studies included a study population with a single stenosis or multiple stenoses, but only a single stenosis suitable for PCI. While measuring FFR across multiple lesions in the same vessel may identify the lesion that is haemodynamically significant, there were no studies identified that demonstrated an improved outcome among patients receiving the FFR guided approach compared with the stress test guided approach.

Overall, in support of FFR testing for indication 1, the key randomised controlled trial (level II evidence) found no overall difference in outcome between the group who did and did not have an intervention in the group with FFR ≥ 0.75, implying it was safe to defer intervention in this group. Less angina appeared to result in this defer strategy than the perform strategy in the group with FFR ≥ 0.75. The usefulness of FFR measurement was supported by other data that found stress testing and FFR measurement having similar accuracy, and that change in management resulted from measuring FFR. It was less clear from high-level evidence whether FFR measurement was more effective than stress testing. However, some lower level evidence (Level III-2 evidence) supported additional benefit being obtained from FFR testing compared with stress testing, although it was less clear if FFR measurement should be a replacement or additional test to stress testing based on these results. These non-randomised studies included a wider group of participants than the RCTs and included patients with multiple stenoses and acute syndromes.

Indication 2: Measurement of FFR and CFR in patients who have received PTCA and/or stenting

Only four studies were identified that met the eligibility criteria for this indication. Three were registry-based studies that did not incorporate any change in management in association with an adverse FFR measurement. The fourth compared using FFR measurement to guide further stenting with a strategy of directly stenting without measuring FFR in a non-randomised design. There was no significant difference in survival at 700 days in this study, but it had only 155 participants. In the other three studies, a low FFR was associated with increased risk of subsequent cardiac events. However, it was unclear if a change in management would improve patient outcome in those with a low FFR.

Cost-effectiveness

Cost-minimisation analysis was used to identify the most cost-effective strategy. This is because the overall conclusion of the effectiveness section was that currently available evidence suggests that patient outcomes would not be different depending on whether FFR measurement was used, stress testing was used, or patients with intermediate lesions on coronary angiography proceed directly to PCI. Costs were estimated based on currently available cost data, including Medicare Benefits Schedule reimbursement fees, AR-DRG data for public and private hospitals, and the manufacturer's price for Radi pressure wire, which is used for FFR measurement. Costs were based on a single lesion.

The expected cost per patient, and therefore total annual costs, are expected to be lower for a strategy of measuring FFR prior to a decision to proceed with PCI than for a strategy of stress testing prior to a decision to proceed with PCI. However, the difference is small compared with the difference between either of these strategies and a strategy of proceeding directly to PCI.

The total costs per patient of the various strategies were estimated to be: proceeding directly to PCI, $9,910; stress testing prior to PCI, $8,014); and of FFR measurement prior to PCI, $7,516. These estimated costs translate into per patient savings associated with the use of FFR measurement of $498 relative to the cost of stress testing and of $2,394 relative to proceeding directly to PCI. As a result, the cost-effectiveness of FFR measurement is greater than that of stress testing and significantly greater than that of proceeding directly to PCI.

The expected total annual cost of performing FFR measurement on all 8,862 patients identified as having intermediate lesions on angiography annually is $66,610,620. This represents annual savings of $4,413,080 relative to performing stress testing on all patients. This difference is small compared with the difference between proceeding directly to PCI and FFR measurement: FFR measurement is associated with a total annual savings of $21,213,049 relative to proceeding directly to PCI.

Due to a lack of evidence regarding the use of FFR measurement post-PCI, only a basic costing was estimated. Estimates are for patients with a single intermediate and severe coronary stenosis. For patients with intermediate coronary stenoses, the estimate is of the incremental direct cost per patient of FFR measurement immediately following a PCI procedure. This assumes that the pressure wire would be used for FFR measurement prior to PCI and could be re-used following PCI. The incremental direct cost per patient of measuring FFR following PCI for patients with intermediate coronary stenoses would be $250. Patients with severe coronary stenoses would not typically have had FFR measurement prior to PCI. For these patients, the use of coronary pressure wire may replace the use of a standard guidewire. The incremental direct cost per patient with severe coronary stenosis is estimated to be approximately $1,360.

Recommendations

1st indication

On the strength of evidence relating to safety, effectiveness and cost-effectiveness, the MSAC recommends that public funding be supported for the use of coronary pressure wires to determine whether revascularisation should be performed on intermediate lesions identified on coronary angiography, where previous stress testing has either not been performed or the results are inconclusive.

2nd indication

On the basis of the limited evidence relating to effectiveness and cost-effectiveness, the MSAC recommends that public funding not be supported for the use of coronary pressure wires to assess the effectiveness of percutaneous coronary interventions.

-The Minister for Health and Ageing accepted these recommendations on 28 March, 2006 -

Appendix A MSAC terms of reference and membership

MSAC's terms of reference 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
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research
Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues
Ms Samantha Robertson	Department representative
Professor Jeffrey Robinson	obstetrics and gynaecology

Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Advisory Panel

Advisory panel for MSAC application 1080

Coronary pressure wire

Assoc. Prof. John Atherton (Chair) MBBS, PhD, FRACP	Member of MSAC
Mr Peter Edwards	Nominee of the Consumers' Health Forum of Australia
Prof. Ken Thomson MD, FRANZCR, FRCR Professor and Director Radiology, The Alfred, Melbourne	MSAC member
Dr Robert Whitbourn MBBS, BMedSc, BSc(Hons) Director of Coronary Care + Director, The Cardiovascular Research Centre, St Vincent's Hospital, Melbourne	Co-opted expert
Dr Stephanie Wilson MBBS(Hons), FRACP, PhD Staff Specialist in Cardiology, Director of CCU, St Vincent's Hospital, Darlinghurst, NSW.	Nominee of the Cardiac Society of Australia and New Zealand

Evaluators

Dr Robert Weir MBChB,MPH(Dist),MSc,FAFPHM	NZHTA
Dr Shelagh Dawson PhD	NZHTA (until September, 2005
Mrs Sarah Hogan MA	Canterbury Economic Consulting
MrsSusan Bidwell MA, MLIS	NZHTA
Dr Ray Kirk PhD	NZHTA (until February 2005)

Department of Health and Aging

Ms Brenda Campe (until March 2006)	Health Technology Section
Ms Marlene Williamson (from March 2006)	Health Technology Section

Appendix C Clinical flow charts

Indication 1: Patients with an intermediate lesion on coronary angiography

Diagram 1: Without pressure wire

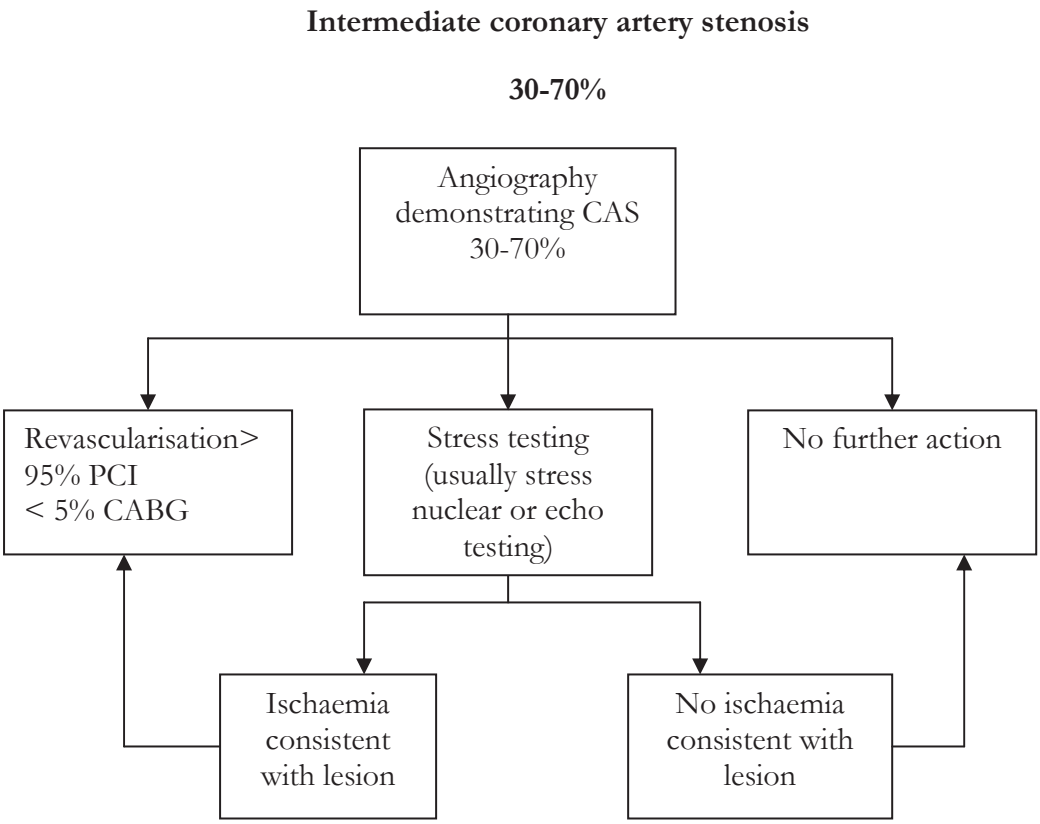
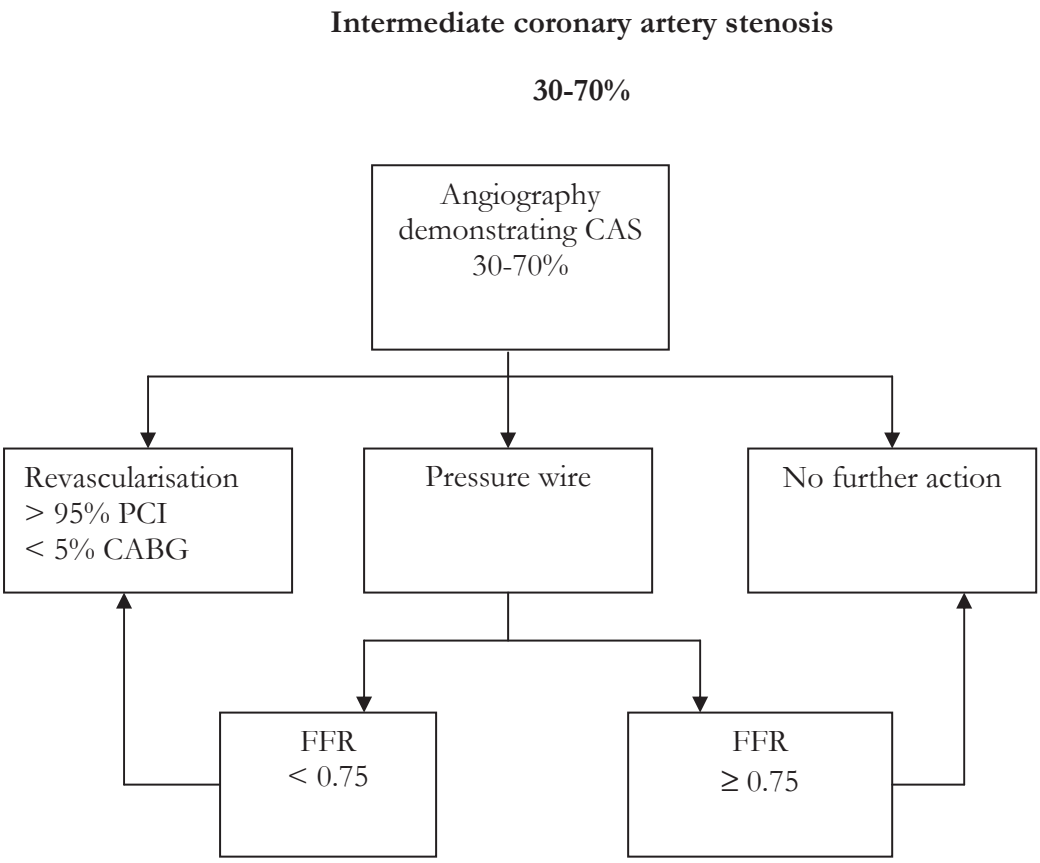


Diagram 2: With pressure wire



Indication 2: Part of PCI procedure

Diagram 1: Without pressure wire

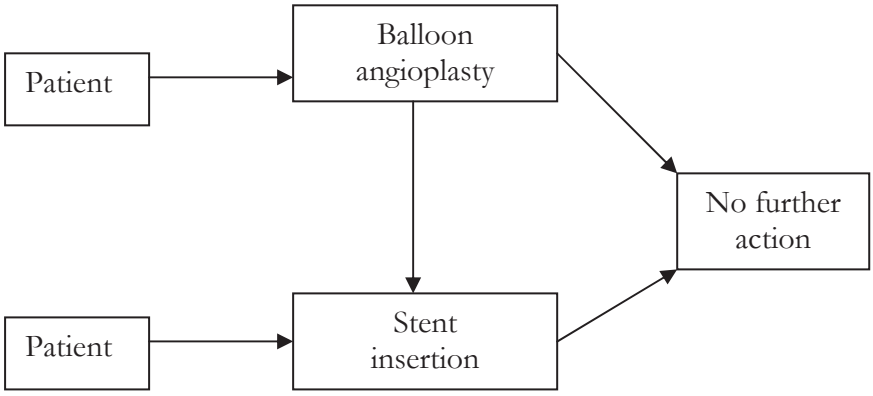
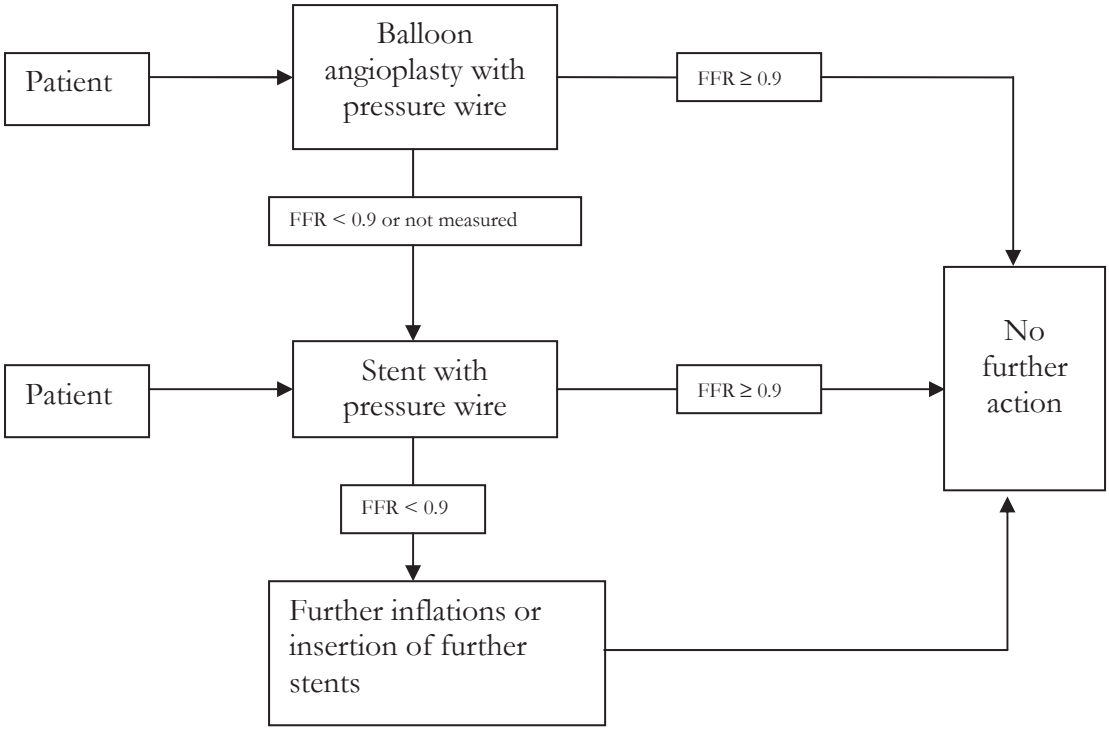


Diagram 2: With pressure wire



* Urgent CABG not included in Diagram 1 or 2 as very small proportion require this intervention 0.1-0.5 %

** All treatment groups will receive optimal secondary prevention strategies

Appendix D Website sources of information

HTA Organisations	Website URL
Agence d'Evaluation des Technologies et des Modes d'Intervention (AETMIS)	http://www.aetmis.gouv.qc.ca/
Agencia de Evaluacion de Tecnologias Sanitarias (AETS)	http://www.isciii.es/unidad/aet/caet.html
Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia (AETSA)	http://www.csalud.junta-andalucia.es/orgdep/AETSA/
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
Agency for Health Research Quality (AHRQ)	http://www.ahrq.gov
L'Agence nationale d'Accréditation et d'Evaluation en Santé	http://www.anaes.fr
L'Agence Nationale pour le Developpement de l'Evaluation Medicale (ANDEM)	http://www.upml.fr/andem/andem.htm
British Columbia Office of Health Technology Assessment (BCOHTA) publications*	http://www.chspr.ubc.ca/cgi-bin/pub
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.aatm.es/
Canadian Coordinating Office for Health Technology Assessment (CCOHTA)	http://www.ccohta.ca
Centre for Clinical Effectiveness, Monash University	http://www.med.monash.edu.au/healthservices/cce/
Center for Medical Technology Assessment (CMT)	http://ghan.imt.liu.se/cmt/
College voor Zorgverzekeringen (CVZ)	http://www.cvz.nl
German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DIMDI)	http://www.dahta.dimdi.de/

* Office closed – publications still available on this link

Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.dihta.dk/
Danish Institute for Health Services Research (DSI)	http://www.dsi.dk/
ECRI (USA)	http://www.ecri.org
Unidad de Tecnologias de Salud (ETESA)	http://www.minisal.cl
EUROSCAN	http://www.ad.bham.ac.uk/euroscan/index.asp
Finnish Office for Health Care Technology Assessment (FinOHTA)	http://www.stakes.fi/finohta/
HAYES Alerts Newsletters	http://www.hayesinc.com
Health Technology Assessment International	http://www.htai.org/
Health Council of the Netherlands (GR)	http://www.gr.nl/
Minnesota Health Technology Advisory Committee (HTAC) publications*	http://www.health.state.mn.us/htac/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Institute of Technology Assessment of the Austrian Academy of Science (ITA)	http://www.oeaw.ac.at/ita/hta/
International Network of Agencies for Health Technology Assessment (INAHTA)	http://www.inahta.org
Medical Technology Assessment Group (M-TAG)	http://www.m-tag.net/
Medical Technology and Practice Patterns Institute	http://www.mtppi.org/
National Coordinating Centre for Health Technology Assessment (NCCHTA)	http://www.soton.ac.uk/~hta
National Horizon Scanning Centre (NHSC)	http://www.bham.ac.uk/PublicHealth/horizon
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
NHS Quality Improvement Scotland	http://www.nhsqis.org/
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.net/sanidad/
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se

* Office closed – publications still available on this link

Norwegian Centre for Health Technology Assessment (SMM)	http://www.oslo.sintef.no/smm/
Swiss Science Council/Technology Assessment (SWISS/TA)	http://www.ta-swiss.ch/
TNO Prevention and Health (TNO)	http://www.tno.nl/homepage.html
University Health Consortium Technology Assessment Monitor	http://www.uhc.edu
Veterans' Affairs Technology Assessment Program (VATAP)	http://www.va.gov/vatap/
WHO Health Technology Assessment Programme (Collaborating Centres)	http://www.who.int/pht/technology_assessment/index.html
Other organisations	
Australian Institute of Health & Welfare (AIHW)	http://www.aihw.gov.au
Australian National Health & Medical Research Council	http://www.health.gov.au/nhmrc/index.htm
Commonwealth Department of Health and Aged Care	http://www.health.gov.au
Centres for Medicare and Medicaid Services (US Health Care Financing Administration)	http://www.hcfa.gov
Health Economics Research Group (Brunel University)	http:// www.brunel.ac.uk/depts/herg
US Federal Drug Administration	http://www.fda.gov
Health Canada	http://www.hc-sc.gc.ca/
UK Department of Health publications	http://www.doh.gov.uk/publications/index.html
US Centers for Disease Control	http://www.cdc.gov
Professional Associations/Societies *(representative only)*	
American Heart Association	http://www.americanheart.org
American College of Cardiology	http://www.acc.org
British Cardiac Society	http://www.bcs.com
Cardiac Society of Australia & New Zealand	http://www.csanz.edu.au
European Society of Cardiology	http://www.escardio.org
and other relevant associations	
Controlled Clinical Trials	http://www.controlled-trials.com/
Clinicaltrials.gov	http://www.clinicaltrials.gov

Appendix E Search strategy

Medline Strategy	
1	(coronary restenosis or coronary stenosis).mp
2	coronary disease/ or exp angina pectoris/ or coronary arteriosclerosis/ or coronary stenosis/ or coronary restenosis/
3	myocardial infarction/
4	angioplasty, transluminal, percutaneous coronary/
5	coronary artery bypass/
6	coronary artery disease.tw. or transplant vasculopathy.mp
7	myocardial revascularization/
8	angioplasty/ or stents/
9	(coronary adj3 intervention$).tw
10	(fractional flow reserve or ffr).mp
11	(coronary flow reserve or cfr).mp.
12	(coronary flow velocity reserve or cfvr).mp
13	radi pressure.af.
14	thermodilution/
15	blood flow velocity/
16	(pressure adj3 (wire or guidewire or catheter or sensor)).tw.
17	or/1-9
18	or/10-16
19	17 and 18
20	limit 19 to yr=1990-2004
21	limit 20 to english
22	(letter or news or editorialP.pt
23	21 not 22
24	animal/
25	human/
26	24 not (24 and 25)
27	23 not 26

Embase Strategy	
1	(coronary stenosis or coronary restenosis).mp
2	restenosis/
3	coronary artery atherosclerosis/ or coronary artery obstruction/ or exp angina pectoris/
4	exp angioplasty/ or percutaneous transluminal angioplasty/ or transluminal coronary angioplasty/
5	exp coronary artery surgery/ or coronary artery bypass graft/ or heart muscle revascularization/
6	heart infarction/
7	stent/
8	(transplant vasculopathy or coronary artery disease).tw.
9	coronary artery disease/
10	or/1-9
11	(fractional flow reserve or ffr).mp
12	(coronary flow reserve or cfr).mp
13	(coronary flow velocity reserve or cfvr).mp.
14	radi pressure.af.
15	thermodilution/
16	blood flow velocity/
17	(pressure adj3 (wire or guidewire or catheter$ or sensor)).tw.
18	or/11-18
19	10 and 18
20	limit 19 to english
21	limit 20 to yr=1990-2004
22	(letter or editorial).pt
23	21 not 22
24	animal/
25	human/
26	24 not (24 and 25)
27	23 not 26

These strategies were adapted for searching the other sources of information, depending on the size of the resource and the availability or otherwise of advanced searching modalities.

Appendix F Data extraction tool

Reference:

Research question/Study aim:

1. Assessed diagnostic performance pre angioplasty/stenting YES/NO
2. Assessed diagnostic performance/prognostic ability post angioplasty/stenting YES/NO

Study design:

Study population:

Inclusion criteria:

(*Please circle*)

1. Single lesion disease
2. Left main coronary artery disease
3. Multivessel coronary artery disease
4. Single vessel, multiple lesion disease
5. Diffuse lesions
6. Myocardial infarction
7. Unstable angina
8. Left ventricular dysfunction
9. Microvascular disease

Other criteria:

Recruitment start date:

Recruitment completion date:

Exclusion criteria:

State:

Location (country):

Participant sampling

Consecutive series: YES/NO/UNCLEAR

Other, state:

Data collection (circle one)

Prospective/retrospective/unclear:

Reference standard

All cause mortality	YES/NO
Cardiac related mortality	YES/NO
Myocardial infarction	YES/NO
Angina	YES/NO
Coronary artery revascularisation	YES/NO
"triple stress test"ing	YES/NO

Tests included:

Comparator

Stress testing by:

Exercise ECG	YES/NO
Stress myocardial perfusion imaging	YES/NO
Stress echocardiography	YES/NO

Other:

Technical specification of pressure wire testing

Radi pressure wire used	YES/NO
Manufacturer's instructions followed	YES/NO/UNCLEAR

Other comments:

Technical specification of reference testing

Technical specification of comparator testing

Description of people performing pressure wire testing

Number performing the testing:

Description of people performing the reference testing

Number performing the testing:

Staff position:

Description of people performing the comparator testing

Number performing the testing:

Staff position:

Blinding between pressure wire and reference (circle)

YES/NO/UNCLEAR

Blinding between Pressure wire and Comparator

YES/NO/UNCLEAR

Methods used for results

Patient relevant outcomes

YES/NO

Categorical measures of accuracy (eg. sensitivity and specificity)

YES/NO

Comparison of continuous results between pressure wire and comparator

YES/NO

Study population characteristics:

Characteristic	All participants	Subgroups		
	n=	n=	N=	n=
Age (years): Median/Mean and range				
Sex Male: number and (%) Female: number and (%)				
Size of stenosis				
Indications for pressure wire testing				
Co-morbid conditions				

Adverse events from pressure wire testing:

Adverse events from comparator testing:

Results of effectiveness:

Measure	Pressure wire	Comparator	P value/95% CI
All cause mortality			
Cardiac related mortality			
Myocardial infarction			
Angina			
Coronary artery restenosis			
CABG			
PTCA			
Readmission for coronary event			
Quality of life			

Studies of diagnostic accuracy:

	Reference standard		Total
Pressure wire	Positive	Negative	
Positive			
Negative			
Total			

Spare table:

	Reference standard		Total
Pressure wire	Positive	Negative	
Positive			
Negative			
Total			

Validity estimates:

	Table 1	Table 2
Sensitivity (95%CI)		
Specificity (95%CI)		
PPV		
NPV		
LR+ (95%CI)		
LR- (95%CI)		
DOR		

Critical appraisal criteria

For classification of study quality:

Level of evidence	Study design
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 pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or 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/post-test

Level of Evidence	Criteria
I	Independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard.
II	Independent, blind or objective comparison but in a set of non-consecutive patients, or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the diagnostic test and the reference standard.
III	Independent blind comparison of an appropriate spectrum, but the reference standard was not applied to all study patients.
IV	Any of: Reference standard was not applied blinded or not applied independently. No reference test applied (case series)

Classify High quality = I, Medium quality= II-III, Poor quality/Insufficient information = IV.

Circle:

High quality = Q1

Medium quality = Q2

Poor quality/Insufficient information = Q3

Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy (circle)?

Yes = C1

Otherwise = CX

For classification of applicable population:

Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?

Interpretation:

Representative subject characteristics (age and sex appropriate for indication, intermediate lesion on angiography: 50-80% stenosis)

Clinical setting (Cardiology)

Classification (circle):

P1 Both representative subjects and setting

P2 One of the two criteria satisfied

P3 Neither criterion satisfied

Appraisal questions (**for accuracy studies comparing pressure wire with a reference standard)**

- Prospective versus retrospective study
- Interpretation of reference test results without knowledge of index test results and interpretation of index test results without knowledge of reference test results

  DOUBLE/SINGLE/NIL/UNCLEAR

If single blinding, who was blinded?

- Handling of uninterpretable and/ or indeterminate results

  CLASSIFIED AS MISCLASSIFIED RESULT: YES/NO/UNCLEAR

- Is the research question appropriate to the review question?

  (satisfies PICO question)

  YES/NO/UNCLEAR

- Are these tests replicable in MSAC setting of interest?

  YES/NO/UNCLEAR

- Is the reference standard likely to correctly classify the target condition?

  YES/NO/UNCLEAR

- Were the tests independent (ie. Not incorporated in) the reference standard?

  YES/NO/UNCLEAR

- Were the same clinical data available when test results were interpreted as would be available when the index test is used as intended in clinical practice?

  YES/NO/UNCLEAR

- Did *all* patients (or a random selection) receive verification using a reference standard of diagnosis?

  YES/NO/UNCLEAR

  If no, % not verified

- Did patients receive the *same* reference standard regardless of the test result?

  YES/NO/UNCLEAR

  If no, % verified using a different method (state method)

- Were withdrawals from the study explained?

  YES/NO/UNCLEAR

  % withdrawals

- If two or more tests are compared, were they assessed independently of each other on all patients (or in randomly allocated patients)?

  YES/NO/UNCLEAR

Studies comparing patient relevant outcomes

- Were inclusion and exclusion criteria reported in sufficient detail to permit replication?

  YES/NO

- Were inclusion and exclusion criteria applied consistently?

  YES/NO/UNCLEAR

- Was sufficient detail provided on the sampling frame/strategy?

  YES/NO

- Were the intervention and comparator sufficiently defined to allow replication of the study?

  YES/NO

- Were participants blind to intervention status?

  YES/NO/UNCLEAR/NOT RELEVANT

- Were those measuring outcome blind to intervention status?

  YES/NO/UNCLEAR/NOT RELEVANT

- Were intervention and comparison groups similar at baseline?

  YES/NO/UNCLEAR/NOT RELEVANT

- If groups were not similar, were differences addressed in analysis/interpretation?

  YES/NO/UNCLEAR/NOT RELEVANT

- Were there likely to be residual differences between intervention and comparison groups that could have important effects on outcomes (confounding)?

  YES/NO/UNCLEAR/NOT RELEVANT

- Did any of the comparison group receive the intervention?

  YES/NO/UNCLEAR/NOT RELEVANT

  If yes, what %?

- Did any of the intervention group receive the comparison?

  YES/NO/UNCLEAR/NOT RELEVANT

  If yes, what %?

- Aside from the intervention/comparator were the two groups treated equally?

  YES/NO/UNCLEAR/NOT RELEVANT

- Was intention-to-treat analysis used?

  YES/NO/UNCLEAR/NOT RELEVANT

- Were there differences in the method of measuring outcome between the intervention and control groups?

  YES/NO/UNCLEAR/NOT RELEVANT

- What level of follow-up was achieved?

  Intervention group:

  Control group:

  Overall:

- Were descriptions of settings and locations of source population, eligible populations and sampling frame/strategy sufficient to determine generalisability?

  YES/NO

- What % of eligibles participated?
- What were the reasons for non-participation?
- Were participants representative of eligible population?

  YES/NO/UNCLEAR

- Were study interventions feasible and affordable in usual practice?

  YES/NO/UNCLEAR

- Was management in the comparison group similar to usual practice?

  YES/NO/UNCLEAR

- Were all important outcomes considered: benefits and harms (not just surrogate outcomes)?

  YES/NO/UNCLEAR

- Was it possible to determine the balance of benefits and harms of study intervention?

  YES/NO

Other comments:

Appendix G Studies included in the review

Table G.1 Studies included under safety

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Abildgaard et al., 1997) Level IV Norway	Case series of patients with FFR measured. Inclusion criteria: Routinely scheduled for PTCA. Uncertainty in angiographic interpretation of stenosis severity. Exclusion criteria: Angiographic signs of intracoronary thrombosis. Ostial stenosis, stenoses close to bifurcations, stenoses distal to tortuous vessels. Contraindication to adenosine. Radi pressure wire 0.018" diameter with IC adenosine (left CA 18 µg, right CA 12 µg).	Total 30 participants. Average age 56 years Age range 34-74 years Male 77% Past history MI 37%	No specific interventions.	Safety related outcomes.	No complications attributed to use of the pressure wire. Five patients had slight and transient feeling of pain or pressure in the chest after adenosine. Three had similar symptoms in the neck.	• No comparison between FFR and stress testing. • Spectrum of patients unclear with lack of risk factor data. • Unclear if consecutive patients were included in the study. • Large size pressure wire used (0.014" is now routine compared with the 0.018" used in this study). • No control group. • Restricted study population. Authors' conclusions: No safety related conclusions.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Bech et al., 2001a) Level II The Netherlands, Belgium and Spain	Partially randomised controlled trial. All patients with FFR < 0.75 had PTCA. Patients with FFR ≥ 0.75 were randomised to either a group with PTCA performed or another group with intervention deferred. All patients had > 50% *de novo* stenosis on angiography in a native coronary artery with reference diameter > 2.5mm and no evidence of reversible ischaemia documented by non-invasive testing in the previous two months. Non-invasive tests were either negative, inconclusive or not performed. Exclusion criteria: Total occlusion of target vessel. Q wave infarction. Unstable angina. Radi pressure wire. IV adenosine 140 μg/kg/min or IC adenosine (15 μg in right coronary artery or 20 μg in left coronary artery).	325 participants (91 in the defer group, 90 in the perform group with FFR ≥ 0.75 and 144 in the perform group with FFR < 0.75). Defer / Perform / FFR<0.75 Average age 61 / 61 / 60 Male 65% / 63% / 80% Smoking 27% / 23% / 29% Hypertension 36% / 34% / 42% Diabetes 15% / 9% / 13% Hyperlipidaemia 43% / 48% / 39% Family history of heart disease 54% / 46% / 45%	Three groups: Group with FFR ≥ 0.75 randomly assigned to the: Defer group or the perform group. Defer group – no intervention performed. Perform group – PTCA performed. All participants with FFR < 0.75 had PTCA.	All cause mortality. MI Coronary artery revascularisation. Primary outcome: Composite measure of coronary events combining the above outcome measures.	In hospital events: Defer group – 0 events Perform group – 5 events FFR < 0.75 – 12 events *P* value (defer versus perform) = 0.03	• No comparison between FFR and stress testing. • Significantly higher proportion of males in the group with FFR < 0.75 (*P*< 0.05). • Age range not presented limiting knowledge of the spectrum of patients. • Unclear if participants were blind to intervention status but measurement of outcome was blind to group assignment. • Intention-to-treat analysis used. • 100% follow-up at 12 months and 98% at 24 months. • Patients with small target arteries were excluded because their inclusion could bias the outcome in favour of the deferral group. • Randomisation performed before FFR measured. • Independent end points committee reviewed all events and analysis was based on the committee's classification of events. • Stenting was conducted in 46/90 in the perform group (51%) and 59/144 in the FFR < 0.75 group (41%). Authors' conclusions: In patients with a coronary stenosis who are referred for PTCA without objective evidence of ischaemia, measurement or coronary pressure just before planned intervention' identified patients with FFR>0.75 who do not benefit from PTCA and patients with FFR< 0.75 in whom PTCA is an appropriate treatment and markedly improves functional class.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Bech et al., 2001b) Level III-2 The Netherlands and Belgium	Cohort study with average follow-up of 2.5 years (range 12-63 months). Inclusion criteria: Left main coronary artery stenosis (40-60%) or left main coronary artery stenosis visible but could not be quantified. No other angiographic abnormalities that warranted CABG. Recruitment: 1994-1999. Radi pressure wire used with IV adenosine 140 µg/kg/min for 2-4 minutes.	Total 54 participants. FFR ≥ 0.75 FFR < 0.75 Average age 60 years 63 years Age range Not stated Not stated Male 75% 87% Smoking 29% 63% Hypertension 17% 30% Diabetes 33% 20% High cholesterol 33% 47% Family history of heart disease 17% 53% Statistically significant difference between groups in proportion of smokers and proportion with family history of heart disease ($P < 0.05$).	Two groups: 1) FFR ≥ 0.75 received no CABG. PTCA of other lesions performed if appropriate. 2) FFR < 0.75 CABG.	All cause mortality. MI Coronary artery revascularisation.	No complications occurred during catheterisation or pressure measurement.	• No comparison between FFR and stress testing. • Age range not presented, limiting knowledge of the spectrum of patients. • All participants received the intervention/control to which they were assigned. • 100% follow-up but unclear if the duration of follow-up was the same in both groups. • The participation rate was unclear. • Significant differences at baseline (more smokers and positive family history in CABG group). Authors' conclusions: In patients with suspected equivocal left main coronary artery disease, intracoronary pressure measurements and calculations of the FFR are feasible and help in decisions between surgical and medical treatment. CABG may be deferred in group with FFR ≥ 0.75. Study underlines the inability of angiography and quantitative coronary angiography to discriminate between physiologically significant and non-significant equivocal left main coronary artery disease.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Bech et al., 1998) Level IV The Netherlands and Belgium	Case series of patients followed for a mean of 18 months. Restricted to patients with FFR ≥ 0.75 and who had further intervention deferred on the basis of the FFR result. Inclusion criteria: Patients referred for intervention of one stenosis in mid or proximal part of native coronary artery. Myocardial territory dependent on the stenosed target vessel was normokinetic. Recruitment: May 1993 to May 1997. Radi pressure wire used with IC adenosine 12-20 µg or IV Adenosine 140 µg/kg/min for 2-4 minutes.	100 participants. Average age 61 years Age range 33-83 years Male 69% Ever smoker 39% Hypertension 37% Diabetes 17% High cholesterol 37% Family history of heart disease 43% Past history MI 6%	No interventions – patients restricted to FFR ≥ 0.75.	Mortality (all cause and cardiac related). MI Angina CABG PTCA	No procedural complications.	• No comparison between FFR and stress testing. • Age range not presented, limiting knowledge of the spectrum of patients. • Restricted to patients with high FFR – an uncontrolled study. • 100% of eligible population participated. • 100% follow-up. • Stress test performed in 64 of the 100 participants and was positive in 28. • Variable follow-up – mean 18 months and > six months in 79%. Authors' conclusions: Retrospective, non-randomised study and lacking comparative data from a group undergoing PTCA. It is not possible to estimate the event rate that would have occurred had PTCA been performed. Nevertheless, it can be concluded that in patients with chest pain who are scheduled for PTCA on an intermediate stenosis, deferral on the basis of FFR > 0.75 is safe, irrespective of the non-invasive stress test result and is associated with a low coronary event rate. To confirm these findings a large, randomised prospective study is underway.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Hernandez Garcia et al., 2001) Level IV Spain	Case series following patients for a mean of 10.7 months (Range 2-24 months). Inclusion criteria: FFR ≥ 0.75 Recent coronary syndromes in whom clinical status had stabilised and no changing ECG abnormalities were present. Exclusion criteria: Moderate to severe lesions and current MI (< four days since onset of symptoms). Significant valve disease. Recruitment: July 1007 to May 1999. Radi pressure wire used with IV Adenosine 140 µg/kg/min for 2 minutes.	Total 43 participants. Average age 58 years Age range 33-78 years Male 79% Unstable angina 56% MI 23% Chest pain post angioplasty 12% Effort angina 9%	No specific intervention (restricted study group).	All cause mortality. MI Angina Coronary artery revascularisation.	No complications during FFR measurements.	• No comparison between FFR and stress testing. • Restricted to patients with high FFR – an uncontrolled study. • Lack of risk factor data limiting knowledge concerning spectrum of patients – spectrum does not represent the group that would be tested with pressure wires in the Australian setting given the limitation to patients with FFR ≥ 0.75. • Variable lengths of follow-up – high risk of selection bias. Authors' conclusions: Results support the safety of deferring PTCA in patients with moderately severe stenosis and FFR ≥ 0.75. Findings suggest that FFR is safe and useful in clinical decision making and may have economic implications that deserve to be investigated in larger prospective series of patients.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Jasti et al., 2004) Level III-2 USA	Cohort study following patients with angiographically ambiguous left main CAD. Excluded criteria: Recent MI. Unstable angina or haemodynamic instability. Significant three vessel disease and Left main CAD. Distal vessels totally occluded. Occurrence of ventricularisation or hypotension during catherisation. Recruitment: Nov 15 2000 to Feb 21 2003. Wavewire used for FFR measurement. IC adenosine 42-56 µg.	Total 55 participants (41 with FFR ≥ 0.75, 14 with FFR < 0.75). Average age 62 years Male Not stated Ejection Fraction 50% Smoking 71% Hypertension 91% Diabetes 36% P.Hx CABG 24%	Two groups: 1) FFR ≥ 0.75 received no intervention. 2) FFR < 0.75 Either PCI or CABG (clear guidelines for determining choice of PCI or CABG).	Mortality (all cause and cardiac related). Admitted for angina. Cardiac event (death, MI, CABG and PCI related to left main CAD or native coronary artery where FFR had previously been performed).	No complications related to the procedures (including FFR, IVUS, PCI and CABG).	• No comparison between FFR and stress testing. • Spectrum of patients unclear with lack of gender breakdown. • Unclear if consecutive patients were selected. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. Lack of blinding could have an influence on decision to admit for angina. • Unclear if both groups were similar at baseline – potential selection bias and potential for confounding. • Four of 41 were excluded from follow up in the group with FFR ≥ 0.75 since they had a CABG during follow up. • Primary purpose of this study was to compare IVUS with FFR. Authors' conclusions: Strong correlation between IVUS and FFR and also a strategy to assess the significance of a LCA stenosis using FFR or IVUS with FFR is safe and superior to angiography.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Jeremias et al., 2000) Level III-2 USA	Study comparing the efficacy of IC and IV adenosine in patients having FFR measured. All patients received both methods of administration (IC route used first). Inclusion criteria: Chest pain referred for diagnostic or interventional cardiac catheterisation. Exclusion criteria: Acute unstable angina. Acute MI. Old MI in territory supplied by target vessel. AV conduction abnormalities. Radi pressure wire used. IC adenosine right CA: 15-20 μg, left CA 18-24 μg. IV adenosine 140 μg/kg/min.	Total 53 participants. Mean age 63 years Age range 31-95 years Male 75%	Study comparing IC and IV administration of adenosine.	Safety related outcomes.	IV dose IC dose Δ heart rate (beats/min) 5.6 0.6 Δ BP systolic -17.3 -3.3 Δ BP diastolic -10.3 -3.2 All differences $P < 0.001$ No adverse events during IC administration. IV administration: One episode of severe bronchospasm. One episode of severe nausea.	• No comparison between FFR and stress testing. • One exclusion due to failure of proper data recording. • Unclear if consecutive patients were used. • Limited dose range tested (higher doses may produce a better hyperemic response). Authors' conclusions: IC bolus of adenosine is a safe and effective alternative compared with continuous IV infusion. In approximately 8%, IC adenosine resulted in an FFR difference of ≥ 0.05 compared with IV infusion. This finding is of critical relevance when FFR is in the range 0.75-0.80. In these cases an additional hyperemic stimulus such as IV adenosine or papaverine should be used. For most patients, there are key advantages related to using IC bolus: ease of use, cost reduction, and excellent safety profile.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Jimenez-Navarro et al., 2004) Level III-2 Spain	Cohort study with mean follow-up of 26 months. Consecutive patients with left main coronary artery stenosis of 30% on angiography. Exclusion criteria: Acute MI within past four days. Cardiogenic shock. Three vessel disease suitable for cardiac surgery. Recruitment: Sept 1997 to Feb 2002. Radi pressure wire used to measure FFR. IV Adenosine 140 µg/kg/min over two minutes for hyperemia.	Total 27 participants (20 with FFR ≥ 0.75, 7 with FFR < 0.75). FFR ≥ 0.75 / FFR < 0.75 Average age: 63 years / 59 years Age range: Not stated / Not stated Male: 75% / 86% Ejection Fraction: 59% / 59% Smoking: 60% / 57% Hypertension: 35% / 42% Diabetes: 20% / 42% High cholesterol: 35% / 57%	Two groups: 1) FFR ≥ 0.75 received no intervention. 2) FFR < 0.75 Coronary revascularisation (one stent, six CABG).	Mortality (all cause or cardiac related). Angina	No complications during measurement of FFR.	• No comparison between FFR and stress testing. • Small sample size. • Age range not presented limiting knowledge of the spectrum of patients. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. • Four of 20 patients in FFR ≥ 0.75 group had a stent implanted in an affected artery other than the left main coronary artery. • Some discrepancy in the number of participants followed up in the FFR ≥ 0.75 group (19 described in the discussion yet there were 20 in the original group). Authors' conclusions: Results suggest the safety of deferring coronary revascularisation in patients with left main coronary artery stenosis and FFR ≥ 0.75. Study emphasises the inability of the percentage of luminal stenosis to differentiate physiologically between significant and no significant stenosis.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Leesar et al., 2003) Level II France	RCT: FFR versus stress testing. Inclusion criteria: Patients with unstable angina or non-ST-segment elevation MI (NSTEMI). Enrolled if episode of angina of > 20 minutes duration or recurrent episodes of angina at rest and at least one of: - new ST depression - transient ST elevation - new T wave inversion in ≥ 2 leads - elevated cardiac markers - history MI - prior coronary artery disease or history of PCI Only enrolled if a single lesion of intermediate severity was identified on coronary angiography. Exclusion criteria: - incessant chest pain not responding to medical therapy. - left main or multi-vessel CAD. - prior CABG. Vessels totally occluded or supplying an akinetic territory. Recruitment: Aug 1999 to March 2001. WaveWire used to measure FFR. IC Adenosine 36-42 μg in left coronary artery, 18-24 μg in right.	Total 70 participants (35 received stress myocardial perfusion imaging and 35 received FFR measurement). Stress testing / FFR Mean age 55 years / 59 years Male 63% / 69% Ejection fraction 53% / 50% Tobacco abuse 43% / 57% Hypertension 74% / 71% Diabetes mellitus 31% / 37% Hyperlipidaemia 63% / 54%	Two groups: 1) Stress testing with stress perfusion scintigraphy. 2) FFR group. FFR ≥ 0.75 or negative stress test – no intervention. FFR < 0.75 or positive stress test – PCI.	Mortality (all cause and cardiac related). MI CABG PTCA Readmission for unstable angina.	There were no complications related to cardiac catheterisation or FFR measurement. There was no significant difference in radiation exposure time between the two groups (FFR nine minutes, stress testing seven minutes). There was no significant difference in amount of contrast media used between groups (FFR group: 182 mls, stress test group 167 mls).	• Comparison between FFR and stress testing. • Age range not presented, limiting knowledge of the spectrum of patients. • Small sample size limiting power to detect a significant difference in outcome between testing procedures. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. • All received assigned intervention. • 97% follow-up in both groups (mean 14 months follow-up in FFR group and 12 months in stress test group). • Method of randomisation unclear. • Limited eligibility criteria. Authors' conclusions: A decision-making strategy based on FFR appears to be superior to one based on stress testing in patients with unstable angina. This needs to be further tested in a large, multi-centre, prospective, randomised trial.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Legalery et al., 2003) Level IV France	Single-centre registry consecutive series of patients with 40-60% diameter stenosis on angiography and a lack of demonstrated myocardial ischaemia. Exclusion criteria: - acute coronary syndrome in last seven days. - contraindication to aspirin or heparin. - LV EF < 35% or LV hypertrophy. - ostial location, serial stenosis or distal occlusion of target artery. Recruitment: Dec 1999 to May 2002. Wavewire used to measure FFR. IC Adenosine 50 μg.	190 participants divided between 122 who had a 4 Fr guiding catheter and 68 with a 7 Fr guiding catheter. Average age 61 years Male 80% Smoking 65% Hypertension 47% Diabetes 25% High cholesterol 78%	Series of patients with FFR measured.	Procedural complications up to 30 days post-procedure. Procedural complications defined as any procedural complication related to or not to the pressure guidewire placement, death, Q- or non-Q wave MI, need for immediate revascularisation or bleeding complications.	No complications with 4 Fr guiding catheter. Results for 7 Fr guiding catheter not presented.	• No comparison between FFR and stress testing. • Age range not presented limiting knowledge of the spectrum of patients. • Lack of effectiveness data so unable to consider balance of benefits and harms when measuring FFR in association with a small guiding catheter (although comparison of values across the two different sizes of catheter showed acceptable agreement). • No blinding. • Single lesions only. • 6% of lesions could not be assessed with the 4Fr catheter.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Lopez-Palop et al., 2004) Level III-2 Spain	Cohort study with one-year follow-up. Consecutive patients with 40-70% diameter stenosis in stent or 5mm adjacent to either of the two edges of the stent. Exclusion criteria: Angiographic study scheduled in an investigational procedure. Instent restenosis lesions in vessels with > 40% stenosis in a segment proximal or distal to the zone where the in stent restenosis was located. Recruitment: Jan 2000 to July 2002. Radi pressure wire and Wavewire used to measure FFR. IC adenosine ≥ 100 μg bolus for hyperemia.	Total 62 participants ((40 with FFR ≥ 0.75, 22 with FFR < 0.75). FFR ≥ 0.75 / FFR < 0.75 Mean age 60 years / 60 years Male 70% / 91% Atypical chest pain 28% / 14% Stable angina 18% / 27% Unstable angina 45% / 55% Non-ST elevation MI 5% / 0% Silent ischaemia 5% / 5% Current smoker 33% / 54% Hypertension 50% / 54% Diabetes 50% / 27% High cholesterol 63% / 68%	Two groups: 1) FFR ≥ 0.75 received no intervention (followed for one year). 2) FFR < 0.75 Coronary revascularisation. 24 lesions: 9 – balloon angioplasty 7 – cutting balloon 2 – brachytherapy 5 – in-stent stenting 1 - CABG	Mortality (all cause or cardiac related). MI Readmission for coronary event (angina or chest pain).	No complications related to the use of the pressure wire were observed.	• No comparison between FFR and stress testing. • Age range not presented, limiting knowledge of the spectrum of patients. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. Authors' conclusions: Angiographic quantification of moderate in stent restenosis has a poor correlation with its functional significance as assessed by FFR. FFR should be considered as the optimum tool to decide on the necessity for re-intervention.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Lopez-Palop et al., 2002) Level IV Spain	Case series of patients who had FFR measured both pre- and post-intervention. Patients were included if the interventional cardiologist considered pressure wire insertion was indicated. Recruitment: Oct 1998 to Nov 2000. Cardiometrics wire used. IC Adenosine 20-200 µg.	190 procedures. Mean age 61 years Age range Not stated Male 77% P. Hx MI 41%	No specific intervention.	Adverse events from pressure wire testing.	One type B coronary dissection.	• No comparison between FFR and stress testing. • Consecutive patients. • 6 or 7 Fr guiding catheter used. • Wide variation in Adenosine dose used. • Eligibility criteria subjective. • Few patient details – spectrum of patients unclear. • Significant potential for selection bias. Authors' conclusions: The pressure guidewire is a useful tool that can be integrated in the daily work of a haemodynamics laboratory. The use of the pressure guidewire is associated with practically no complications and with a significant but small prolongation of the procedures. However, it provides information for effective decision-making based on functional data that complement the morphological data obtained during angiography.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Muramatsu et al., 2002) Level III-2 Japan	Cohort study based on FFR level after PTCA. Patients restricted to those with recent MI who had adequate wave patterns when using the pressure wire. Wavewire used. Medication to achieve maximal hyperaemia was not stated.	Total of 155 participants (37 with FFR ≥ 0.94, 40 with FFR < 0.94 following PTCA, 78 in control group where FFR was not measured). FFR Measured / Control Group Average age: 62 years / 64 years Age range: Not stated / Not stated Male: 79% / 73% Smoking: 29% / 36% Diabetes mellitus: 16% / 19% Hyperlipidaemia: 23% / 26% Left anterior descending disease: 62% / 40%	Three groups: 1) FFR ≥ 0.94. No further treatment given. 2) FFR < 0.94. Stent inserted. 3) Directly stented without measuring FFR (control group).	Reocclusion and restenosis.	Acute post-procedural reocclusion 0%. Reocclusion at discharge: 1.7% in FFR group, 0% in controls. Restenosis at discharge: 5.1% in FFR group, 0% in controls. No in-hospital CABG or death.	• No comparison between FFR and stress testing. • Age range not presented, limiting knowledge of the spectrum of patients. • Baseline differences between study groups, with significantly more participants in the FFR groups than the control group having left anterior descending disease. • Blinding status unclear. • Level of follow-up unclear. • Non consecutive patients. • Non-uniformity in stent used – multilink stent used in 80% of the FFR group and 68% of the control group. • Low power to detect difference in survival.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Ogawa et al., 2004) Level IV Japan	Children with Kawasaki disease who had at least one coronary lesion. Radi pressure wire used with IV papaverine (left CA 0.3 mg/kg to maximum 12 mg, right CA 0.2 mg/kg to a maximum of 8mg).	Total 128 patients. Average age 6 years Age range 1-15 years Male 77%	No interventions.	Safety related outcomes.	Procedures were performed safely in all subjects.	• No comparison between FFR and stress testing. • Unclear if consecutive patients were selected. • Young age group. • No comparison group. Authors' conclusions: No safety specific conclusions.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Ozdemir et al., 2002) Level IV Turkey	Followed patients with FFR ≥ 0.75 to MI or death. Mean follow-up 16.6 months (minimum 6 months). Patients with intermediate coronary stenoses (30-70% diameter stenosis by quantitative coronary angiography). FFR ≥ 0.75 in at least one major epicardial coronary artery. Recruitment: June 1999 to Dec 2000. Radi pressure wire used (mean of two measurements). IC Adenosine (30 μg for left coronary artery, 20 μg for right).	51 participants. Mean age 54 years Age range 31-72 Male 82% Atypical angina 19% Typical stable angina CCS class 1 2% CCS class 2 27% CCS class 3 8% Unstable angina 18% Post MI 14% Positive stress test 12% Ejection fraction 63% Hypertension 41% Diabetes mellitus 16%	No specific intervention.	Mortality (all cause or cardiac). MI Target vessel revascularisation.	No complications with respect to either the guiding catheter or pressure wire manipulation or IC adenosine.	• No comparison between FFR and stress testing. • Appropriate spectrum of patients. • No comparison between FFR ≥ 0.75 and FFR < 0.75 (restricted to FFR ≥ 0.75). Therefore of very limited usefulness when considering impact of FFR measurement on outcome. • Unclear if consecutive patients were used. • Level of follow-up not stated. • Lesions in other coronary arteries with stenosis >70% were revascularised (n=18, 35% of sample). • Only 20 of the 51 participants had a stress test. Authors' conclusions: The absence of thallium scan results in 40% of the lesions means it is not possible to come to a firm conclusion about the value of perfusion scan data to predict the clinical behaviour of intermediate coronary stenoses.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Pijls et al., 2002b) Level III-2 USA (five centres) Europe (five centres) Asia (five centres)	Registry study analysed like a case control study at 6 months of follow-up. Explored relationship between post-stent FFR and clinical events. Enrolled in registry if undergoing coronary stenting and a pressure wire was used. Pressure wire was used if an intermediate lesion was present or if multiple stenoses were present. No exclusion criteria. Recruitment: Jan 2000 to April 2001. Radi pressure wire used. Maximal hyperemia achieved using IC Adenosine or IC ATP or IV Adenosine or IV ATP or IC papaverine.	744 participants (668 had no events, 76 with at least one event). No events / Events Average age: 62 years / 60 years Age range: Not stated / Not stated Male: Not stated / Not stated Smoking: 47% / 55% Hypertension: 50% / 56% Diabetes: 23% / 32% High cholesterol: 60% / 70% F. hx of heart disease: 39% / 34%	FFR measured post-stenting.	All cause mortality. MI PCI CABG	No complications attributable to the pressure measurement occurred in any patients.	• Unable to assess the impact of change in management on health outcome in this study population (unclear if additional interventions would have reduced adverse outcomes in the participants with low FFR values post stenting). • Age range and gender not presented limiting knowledge of the spectrum of patients. • Blinding status not stated. • Overall follow up at 6 months 99.2%. • First event for patient counted. • Potential selection bias due to selection of patients with favourable prognosis (less plaque burden). • Unable to measure FFR post stenting in five patients. Authors' conclusions: Coronary pressure measurement is an easy, rapid and relatively cheap method to evaluate stent implantation and to predict occurrence of adverse events within six months of follow up.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Pijls et al., 2002a) Level IV The Netherlands and Belgium	Case series providing safety data relevant to this review. Patients referred for physiological assessment of at least one coronary stenosis. Radi pressure wire used to measure FFR and CFR. IC adenosine 140 µg/kg/min or IC papaverine 15-20 mg.	50 participants (119 lesions). Average age 55 years Age range Not stated Male 82%	No specific interventions.	Comparison of CFR using thermodilution and Doppler methods. Procedural complications.	The studies were uneventful in all patients.	• No comparison between FFR and stress testing. • Few details about study population so spectrum of patients was unclear. • Use of consecutive patients was not stated. • Blinding status unclear. Authors' conclusions: Study shows the feasibility of simultaneous measurement of FFR and CFR by a single guidewire.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Pijls et al., 2000) Level IV The Netherlands and Belgium	Study examining patients with multi-lesion disease in the same vessel. Compared the estimated FFR of stenoses before removal of all stenoses with the actual measured FFR in subsequent lesions after removal of first stenosis. Inclusion criteria: Referred for PTCA of a native coronary artery with ≥ 2 stenoses with ≥ 50% diameter narrowing by visual estimation, separated by an apparently normal segment of ≥ 2 cm in length without a side branch. Radi pressure wire used with IV 140 µg/kg/min over approximately two minutes.	Total 32 participants. Average age 61 years Age range Not stated Male 78%	Estimated FFR versus actual FFR in patients with multi stenoses.	Complications resulting from FFR measurement. Comparison of estimated and actual FFR.	One type B dissection, which did not obstruct flow and was left untreated. No further complications.	• No comparison between FFR and stress testing. • Unclear if consecutive patients were used. • Spectrum of patients unclear (lack of risk factor and age range data). • Adverse events not pre specified. • Primary purpose of study was to assess a method of estimating FFR in sequential stenoses. Authors' conclusions: Method proposed facilitates the selection of PTCA and minimises unnecessary additional procedures on haemodynamically insignificant lesions, which would increase the risk of complications or restenosis.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Pijls et al., 1995) Level IV The Netherlands	Comparison of FFR and exercise testing. Sufficient information for safety component of review. Inclusion criteria: Accepted for elective PTCA with stable angina. Single-vessel disease. Normal LV function. Positive exercise test within 24 hours of PTCA. Also had a group of five participants with normal coronary arteries. Radi pressure wire 0.018" diameter. IV adenosine 140 µg/kg/min.	Total 65 participants. Abnormal coronary artery / Normal coronary artery Average age 57 / 55 Age range 39-74 / 50-60 Male 68% / 80%	No intervention.	Safety related outcomes.	No complications occurred in the 65 participants. Some chest discomfort was experienced with adenosine infusion.	• No comparison between FFR and stress testing. • Consecutive patients. • Spectrum of patients unclear with lack of risk factor data. • Participation rate unclear. • Large size pressure wire used (0.014" is now routine compared with the 0.018" used in this study). Authors' conclusions: No safety specific conclusions.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Reczuch et al., 2004) Level III-2 Poland	Cohort study with mean follow-up of 15 months. Patients with stable angina and borderline lesions (reduction in diameter by 50-70% visually) in ≥ 2 epicardial arteries. Exclusion criteria: Acute coronary syndrome during the six months preceding the study. Heart failure or LVEF < 50%. Coronary lesions localised in vessels with diameter < 2.5mm. Two lesions in same vessel. Presence of aorto-coronary lesions. Appears Wavewire was used to measure FFR. IC adenosine 30 or 60 µg bolus for hyperemia.	Total 16 participants (8 with FFR > 0.75, 8 with FFR < 0.75). Average age 60 years Male 69% Smoking (current) 19% Hypertension 75% Diabetes, type 2 25% Past history of MI 44%	Two groups: 1) FFR > 0.75 received no intervention (followed for one year). 2) FFR < 0.75 PCI: Four of eight received a stent.	Reintervention (CABG or PTCA).	No peri-procedural nor in-hospital complications occurred.	• No comparison between FFR and stress testing. • Age range not presented limiting knowledge of the spectrum of patients. • Unclear if both groups were similar at baseline – potential selection bias and potential for confounding. • Small sample size. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. • Unclear if consecutive patients were selected and the proportion of eligible patients who participated was not stated. • Median follow-up in no intervention group was 15 months compared with 17 months in intervention group. Authors' conclusions: Decision not to perform revascularisation based on FFR measurement is associated with good clinical outcomes. Use of FFR prevents unnecessary revascularisation procedures.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Reczuch et al., 2003) Level IV Poland	Case series examining patients receiving various doses of IC adenosine to obtain maximal hyperemia. WaveWire used.	Total 36 participants. Age 36 years Male 64% Hypertension 64% Type 2 diabetes 22% Current smoker 25% Ex-smoker 36%	Doses of IC adenosine ranging from 30 μg to 90 μg.	Complications resulting from FFR measurement.	"No significant side effects were noted except a transient, self-terminating episode of a second degree atrio-ventricular block in one patient". The patient received 60 μg IC adenosine.	• No comparison between FFR and stress testing. • Unclear if consecutive patients were included. • Small sample size. Authors' conclusions: An increase of the adenosine dose from 30 μg to 60 μg was well tolerated and caused further decrease in the FFR values that may be of clinical importance in some patients. The use of 90 μg adenosine did not further decrease FFR.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Rieber et al., 2002b) Level III-2 Germany	Cohort study with one-year follow-up. Inclusion criteria: Referred for diagnostic coronary angiography for clinically suspected CAD. Target lesion 50-75% diameter stenosis. Negative, inconclusive or missing stress test. Target lesion suitable for PCI. Patients with multi-vessel disease were included provided there was no other lesion suitable for PCI beyond the target vessel. Exclusion criteria: Significant left main disease. Acute coronary syndromes. WaveWire or Radi pressure wire or were used with IC Adenosine 120 µg.	Total 97 participants. FFR ≥ 0.75 / FFR < 0.75 Average age: 65 years / 65 years Age range: Not stated / Not stated Male: 73% / 73% Ejection Fraction: 61% / 61% Current smoker: 9% / 15% Hypertension: 69% / 83% Diabetes mellitus: 15% / 15% High cholesterol: 75% / 87% Past history MI: 41% / 44%	Two groups: 1) FFR ≥ 0.75 received no intervention (followed for one year). 2) FFR < 0.75 received PCI.	Mortality (all cause and cardiac related). MI Coronary artery revascularisation.	FFR measured successfully in all patients. Eight of 107 patients (7%) had a transient AV block after adenosine introduced into the right coronary artery. No other procedural complications.	• No comparison between FFR and stress testing. • Age range not presented, limiting knowledge of the spectrum of patients. • Unclear if consecutive patients were used. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. • 96% follow-up at 12 months. • 37 of 48 (77%) in the PCI group received a stent. • Potential confounding with more complex lesions in the intervention group. • Potential underestimation of adverse events due to missing silent MIs. • 23 of the FFR < 0.75 group had non-pathologic or non diagnostic stress tests indicating useful data from FFR. Authors' conclusions: Deferring patients from PCI if FFR is not critically reduced is a safe option even in patients with coronary multi-vessel disease and complex coronary lesions.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Takagi et al., 1999) Level III-2 Japan	Comparison of quantitative coronary angiography, IVUS and FFR measurements. Provides safety information about FFR measurement. Inclusion criteria: Patients with single lesion or multi-vessel disease. Studied at diagnostic catheterisation or before catheter intervention. Each vessel studied had an isolated stenosis. Radi pressure wire used with IC papaverine (right coronary artery 10 mg, left coronary artery 12 mg).	Total 42 participants. Average age 60 years Age range Not stated Male 88% Past history MI 69%	No interventions. Comparison of coronary angiography, IVUS and FFR.	Adverse events related to the procedures.	Successfully performed without serious complications. Moderate QT prolongation in two patients – normalised spontaneously within one minute.	• No comparison between FFR and stress testing. • Consecutive patients. • Some lack of clarity about defining "serious complications". • Size of guiding catheter used was not stated. Authors' conclusions: No safety related conclusions given.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Takeuchi et al., 1997) Level IV Japan	Comparison of FFR and quantitative coronary angiography. Sufficient data to consider safety of FFR measurement. Inclusion criteria: Undergone elective coronary angiography. Exclusion criteria: MI within two weeks. Unstable angina. Venture II pressure wire used with IC ATP (50 µg left CA, 20 µg right CA).	Total 20 participants. Average age 59 years Age range 36-73 Male 75%	No intervention.	Safety related outcomes.	Pressure measurements could not be obtained in one participant (one vessel) before angioplasty due to severe chest pain in association with ST elevation when the infusion catheter was advanced. No complications occurred during measurement of pressure change or ATP administration.	• No comparison between FFR and stress testing. • Consecutive patients. • Spectrum of patients unclear with lack of risk factor data. However, mainly single-lesion disease. • Unclear if prospective or retrospective study. • Small sample size. Authors' conclusions: No safety related conclusions.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Tamita et al., 2002) Level IV Japan	Case series comparing post-intervention FFR, IVUS parameters and thrombolysis on myocardial infarction grade. Provides safety data about pressure measurement. Patients with their first MI who had single-lesion disease and were successfully treated with recanalisation by PCI within 12 hours of onset of symptoms. Successful treatment defined as < 25% stenosis after PCI. Exclusion criteria: Valvular heart disease. Primary myocardial disease. Cardiogenic shock. Radi pressure wire or WaveWire used. IV Adenosine 0.14 mg/kg/min.	48 participants (including controls who also had FFR measured). Mean age 63 years Age range 46-78 Male 77%	All had coronary pressure measurement.	Procedural complications.	Coronary pressure could be measured in all cases without complications (n=48).	• No comparison between FFR and stress testing. • Patients a mix of acute MI and angina (the latter were undergoing elective PCI). • Consecutive patients used. • Potential adverse events considered were not specified. • Small sample size.

Table G.1 Studies included under safety (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Van der Voort et al., 1996) Level III-2 The Netherlands	Comparison of adenosine and papaverine among patients having FFR measured. Sufficient data for consideration of safety. Inclusion criteria: Intermediate coronary stenosis (50-70%) in proximal or mid part of coronary artery with a reference diameter ≥ 3 mm. Normal AV conduction and normal QT interval. Radi pressure wire 0.018" diameter. IV adenosine 140 µg/kg/min. IC papaverine (12 mg left coronary artery, 10 mg right coronary artery).	Total 24 participants. Average age 53 years Age range 44-72 years Male 54%	No specific intervention.	Safety related outcome measures.	Adenosine Papaverine ΔBP (mmHg) -8 -6 Δ heart rate (beats/ minute) +8 +1 Adenosine: Most patients had a burning, angina like sensation in chest or neck which disappeared after stopping the infusion. Papaverine: Some prolongation in QT time observed in most patients.	• No comparison between FFR and stress testing. • Unclear if consecutive patients were selected. • Spectrum of patients unclear with lack of risk factor data. • Adenosine used first in all participants – unclear if there could be any interaction resulting in increased side effects recorded in the papaverine arm. • Large size pressure wire used (0.014" is now routine compared with the 0.018" used in this study). Authors' conclusions: Adenosine fulfils desirable characteristics of an agent to produce maximum hyperemia, including no important side-effects.

Table G.2 Studies included under effectiveness for indication 1

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Bech et al., 2001a) Level II The Netherlands, Belgium and Spain	Partially randomised controlled trial. All patients with FFR < 0.75 had PTCA. Patients with FFR ≥ 0.75 were randomised to either a group with PTCA performed or another group with intervention deferred. All patients had > 50% *de novo* stenosis on angiography in a native coronary artery with reference diameter > 2.5mm and no evidence of reversible ischaemia documented by non-invasive testing in the previous two months. Non-invasive tests were either negative, inconclusive or not performed. Exclusion criteria: Total occlusion of target vessel. Q wave infarction. Unstable angina. Radi pressure wire. IV adenosine 140 µg/kg/min or IC adenosine (15 µg in right coronary artery or 20 µg in left coronary artery).	325 participants (91 in the defer group, 90 in the perform group with FFR ≥ 0.75 and 144 in the perform group with FFR < 0.75). Defer / Perform / FFR<0.75 Average age 61 / 61 / 60 Male 65% / 63% / 80% Smoking 27% / 23% / 29% Hypertension 36% / 34% / 42% Diabetes 15% / 9% / 13% Hyperlipidaemia 43% / 48% / 49% Family history of heart disease 56% / 46% / 45%	Three groups: Group with FFR ≥ 0.75 randomly assigned to the: Defer group or the perform group. Defer group – no intervention performed. Perform group – PTCA performed. All participants with FFR < 0.75 had PTCA.	All cause mortality. MI Coronary artery revascularisation. Primary outcome: Composite measure of coronary events combining the above outcome measures.	Event-free survival at 24 months: Defer group 89%. Perform group 83%. FFR < 0.75 78%. *P* value (defer versus perform) = 0.27. *P* value (defer versus FFR < 0.75) = 0.03. Free from angina at 24 months significantly higher in defer than perform group (*P* = 0.02).	• No comparison between FFR and stress testing. • Significantly higher proportion of males in the group with FFR < 0.75 (*P* < 0.05). • Age range not presented limiting knowledge of the spectrum of patients. • Unclear if participants were blind to intervention status but measurement of outcome was blind to group assignment. • Intention-to-treat analysis used. • 100% follow-up at 12 months and 98% at 24 months. • Patients with small target arteries were excluded because their exclusion could bias the outcome in favour of the deferral group. • Randomisation performed before FFR measured. • Independent end points committee reviewed all events and analysis was based on the committee's classification of events. • Stenting was conducted in 46% of the perform group and 59% of the FFR < 0.75 group (41%). Authors' conclusions: In patients with a coronary stenosis who are referred for PTCA without objective evidence of ischaemia, measurement of coronary pressure just before planned intervention identified patients with FFR > 0.75 who do not benefit from PTCA and patients with FFR < 0.75 in whom PTCA is an appropriate treatment and markedly improves functional class.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Bech et al., 2001b) Level III-2 The Netherlands and Belgium	Cohort study with average follow-up of 2.5 years (range 12-63 months). Inclusion criteria: Left main coronary artery stenosis (40-60%) or left main coronary artery stenosis visible but could not be quantified. No other angiographic abnormalities that warranted CABG. Recruitment: 1994-1999. Radi pressure wire used with IV adenosine 140 µg/kg/min for 2-4 minutes	Total 54 participants (FFR ≥ 0.75 n=24, FFR < 0.75 n=30). FFR ≥ 0.75 / FFR < 0.75 Average age: 60 years / 63 years Age range: Not stated / Not stated Male: 75% / 87% Smoking: 29% / 63% Hypertension: 17% / 30% Diabetes: 33% / 20% High cholesterol: 33% / 47% Family history of heart disease: 17% / 53% Statistically significant difference between groups in proportion of smokers and proportion with family history of heart disease ($P < 0.05$).	Two groups: 1) FFR ≥ 0.75 received no CABG. PTCA of other lesions performed if appropriate. 2) FFR < 0.75 CABG.	All cause mortality. MI Coronary artery revascularisation.	FFR ≥ 0.75 / FFR < 0.75 Three year survival: 100% / 97% Cardiac event free survival: 76% / 83% Mean CCS angina class Baseline: 2.8 / 3.4 Last follow up: 1.6 / 1.5 $P<0.001$ / $P<0.001$	• No comparison between FFR and stress testing. • Age range not presented limiting knowledge of the spectrum of patients. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. • All participants received the intervention/control they were assigned to. • 100% follow-up but unclear if the duration of follow-up was the same in both groups. • The participation rate was unclear. • Significant differences at baseline (More smokers and positive family history in CABG group). • FFR ≥ 0.75 group: 16 received drugs alone, 7 had PTCA for concomitant lesion and 1 had an aortic valve replacement. • Events in CABG group occurred early whereas they were spread over the follow-up period in the medical group. Authors' conclusions: In patients with suspected equivocal left main coronary artery disease, intracoronary pressure measurements and calculations of the FFR are feasible and help in decisions between surgical and medical treatment. CABG may be deferred in group with FFR ≥ 0.75.Study underlines the inability of angiography and quantitative coronary angiography to discriminate between physiologically significant and non-significant equivocal left main coronary artery disease.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Bech et al., 1998) Level IV The Netherlands and Belgium	Case series of patients followed for a mean of 18 months. Restricted to patients with FFR ≥ 0.75 and who had further intervention deferred on the basis of the FFR result. Inclusion criteria: Patients referred for intervention of one stenosis in mid or proximal part of native coronary artery. Myocardial territory dependent on the stenosed target vessel was normokinetic. Recruitment: May 1993 to May 1997. Radi pressure wire used with IC adenosine 12-20 µg or IV Adenosine 140 µg/kg/min for 2-4 minutes.	100 participants. Average age 61 years Age range 33-83 years Male 69% Ever smoker 39% Hypertension 37% Diabetes 17% High cholesterol 37% Family history of heart disease 43% Past history MI 6%	No interventions – patients restricted to FFR ≥ 0.75.	Mortality (all cause and cardiac related). MI Angina CABG PTCA	KM survival (42 months): 97%. KM free from death or target vessel related outcome (42 months): 84%. KM free from death or any coronary event (42 months): 78%.	• No comparison between FFR and stress testing. • Restricted to patients with high FFR – an uncontrolled study. • 100% follow-up. • Potential measurement error resulting from use of large guiding catheter in some patients may have resulted in inappropriate deferment. • Stress test performed in 64 of the 100 participants and was positive in 28. • Variable follow-up – mean 18 months and > six months in 79%. Authors' conclusions: Retrospective, non-randomised study lacking comparative data from a group undergoing PTCA. It is not possible to estimate the event rate that would have occurred had PTCA been performed. Nevertheless, it can be concluded that in patients with chest pain who are scheduled for PTCA on an intermediate stenosis, deferral on the basis of FFR > 0.75 is safe, irrespective of the non-invasive stress test result and is associated with a low coronary event rate. To confirm these findings a large, randomised prospective study is underway.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Botman et al., 2004) Level III-2 The Netherlands	Cohort study following patients for two years. Referred for CABG because of angiographic multivessel disease. Suitable for both CABG and PCI. Radi pressure wire used. All measurements performed twice and a pressure pullback performed to verify appearance and disappearance of hyperemic gradient at site of lesion. IV adenosine 140 μg/kg/min for hyperemia.	Total 150 participants (87 received CABG and 63 received PCI). CABG PCI Average age 63 years 65 years Age range 37-81 44-79 Male 70% 70% Two vessel disease 46% 44% Three vessel disease 54% 56% Ejection fraction 62% 62% Smoking 41% 49% Hypertension 29% 29% Diabetes 24% 24% High cholesterol 72% 63% Family history of heart disease 47% 54%	Two groups: 1) Three arteries with significant stenosis (FFR ≤ 0.75) or two arteries including proximal LAD received CABG 2) All other patients received PCI	All cause mortality. Myocardial infarction. Angina CABG PTCA	PCI (%) CABG (%) All cause mortality 0 2.3 MI 3.2 4.6 Angina 16 18 CABG 4.8 3.4 PTCA 11.2 8.1 MACE 19.1 18.4 No significant difference in any outcomes between the two groups.	• No comparison between FFR and stress testing. • Spectrum of patients limited to FFR ≤ 0.75. Appropriate demographic composition. • Unclear if consecutive patients were selected. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. • Both groups similar at baseline. • 100% follow-up. • 21 of 270 bypasses were based on cardiac surgeon opinion rather than FFR. Authors' conclusions: In patients with multi-vessel disease, coronary pressure measurement and calculation of FFR are useful tools to identify, which of several stenoses are functionally significant and contribute to reversible ischaemia. Using this approach, a considerable number of patients referred for CABG can be treated with PCI.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Chamuleau et al., 2002) Level III-2 The Netherlands	Cohort study with one- year follow- up. Patients selected with stable or unstable angina (Braunwald's Classification I or II), multivessel CAD and one intermediate narrowing (40-70% diameter stenosis) provided there was no perfusion defect in the area of interest on SPECT testing. Exclusion criteria: Factors precluding dipyridamole infusion and/or assessment of intracoronary pressure. Factors influencing coronary haemodynamic parameters. Radi pressure wire used. IC Adenosine 15-20 μg.	Total 107 participants (92 with FFR ≥ 0.75, 15 with FFR < 0.75). FFR ≥ 0.75 / FFR < 0.75 Mean age 61 years / 62 years Age range 34-80 / 35-78 Male 72% / 87% Smoking (current) 26% / 20% Diabetes, Type 2 12% / 0% Hyperlipidaemia 60% / 53% Hypertension 40% / 13% P. Hx MI 41% / 53%	No specific intervention. All patients followed for one year whether FFR was ≥ 0.75 or < 0.75.	Occurrence of at least one of the following: Cardiac death MI PTCA of the intermediate stenosis CABG	FFR ≥ 0.75 / FFR < 0.75 Events 8.7% / 26.7% 95% CI 4.1-16.9 / 8.9-55.2 *P* = 0.04 Nine of 12 events were revascularisation procedures and the remaining three events were MIs.	• Participants restricted to patients with no perfusion defect on stress testing. • Appropriate spectrum of patients. • Unclear if consecutive patients were used. • Measurement of outcome was blind to FFR level. • 100% follow-up at one year. • Results imply a difference in event rate based on different FFR levels and also imply additional useful information in this group of SPECT negative patients. However, it does not provide information about the impact of any change in management as a result of the FFR results. Authors' conclusions: These data suggest that FFR is more useful than SPECT for clinical decision making and risk stratification of an intermediate stenosis in patients with multi-vessel CAD.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Hernandez Garcia et al., 2001) Level IV Spain	Case series following patients for a mean of 10.7 months (range 2-24 months). Inclusion criteria: FFR ≥ 0.75. Recent coronary syndromes in whom clinical status had stabilised and no changing ECG abnormalities were present. Exclusion criteria: Moderate to severe lesions and current MI (< four days since onset of symptoms). Significant valve disease. Recruitment: July 1997 to May 1999. Radi pressure wire used with IV Adenosine 140 µg/kg/min for 2 minutes.	Total 43 participants. Average age 58 years Age range 33-78 years Male 79% Unstable angina 56% MI 23% Chest pain post Angioplasty 12% Effort angina 9%	No specific intervention (restricted study group).	All cause mortality. MI Angina Coronary artery revascularisation.	Five of 43 patients (12 per cent): coronary artery revascularisation (three in the same artery as the one under study). Kaplan-Meier one-year event-free survival 93.2%.	• No comparison between FFR and stress testing. • Restricted to patients with high FFR – an uncontrolled study. • Lack of risk factor data, limiting knowledge concerning spectrum of patients – spectrum does not represent the group that would be tested with pressure wires in the Australian setting given the restriction to patients with high FFR. • Variable lengths of follow-up – high risk of selection bias. Authors' conclusions: Results support the safety of deferring PTCA in patients with moderately severe stenosis and FFR ≥ 0.75. Findings suggest that FFR is safe and useful in clinical decision making and may have economic implications that deserve to be investigated in larger prospective series of patients.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Jasti et al., 2004) Level III-2 USA	Cohort study following patients with angiographically ambiguous Left main CAD. Excluded criteria: Recent MI. Unstable angina or haemodynamic instability. Significant three-vessel disease and left main CAD. Distal vessels totally occluded. Occurrence of ventricularisation or hypotension during catherisation. Recruitment: Nov 15 2000 to Feb 21 2003. WaveWire used for FFR measurement. IC adenosine 42-56 µg.	Total 55 participants (41 with FFR ≥ 0.75, 14 with FFR < 0.75). Average age 62 years Male Not stated Ejection fraction 50% Smoking 71% Hypertension 91% Diabetes 36% P.Hx CABG 24%	Two groups: 1) FFR ≥ 0.75 received no intervention. 2) FFR < 0.75 Either PCI or CABG (clear guidelines for determining choice of PCI or CABG).	Mortality (all cause and cardiac related). Admitted for angina. Cardiac event (death, MI, CABG and PCI related to left main CAD or native coronary artery where FFR had previously been performed).	FFR ≥ 0.75 FFR < 0.75 All cause mortality 8.1% 0% Cardiac Mortality 0% 0% Admitted for Angina 8.1% 0% KM event free survival (38 months) 90% 100% No significant difference in event-free survival.	• No comparison between FFR and stress testing. • Spectrum of patients unclear with lack of gender breakdown. • Unclear if consecutive patients were selected. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. Lack of blinding could have an influence on decision to admit for angina. • Unclear if both groups were similar at baseline – potential selection bias and potential for confounding. • Four of 41 were excluded from follow- up in the group with FFR ≥ 0.75 since they had a CABG during follow-up. • Primary purpose of this study was to compare IVUS with FFR. Authors' conclusions: The present study demonstrates strong correlation between IVUS and FFR and also demonstrates that a decision making strategy to assess the significance of a left main coronary artery stenosis using FFR (cut point of 0.75) or IVUS with FFR is safe and superior to angiography.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Jimenez-Navarro et al., 2004) Level III-2 Spain	Cohort study with mean follow-up of 26 months. Consecutive patients with left main coronary artery stenosis of 30% on angiography. Exclusion criteria: Acute MI within past four days. Cardiogenic shock. Three-vessel disease suitable for cardiac surgery. Recruitment: Sept 1997 to Feb 2002. Radi pressure wire used to measure FFR. IV Adenosine 140 µg/kg/min over two minutes for hyperemia.	Total 27 participants (20 with FFR ≥ 0.75, 7 with FFR < 0.75). FFR ≥ 0.75 / FFR < 0.75 Average age: 63 years / 59 years Age range: Not stated / Not stated Male: 75% / 86% Ejection fraction: 59% / 59% Smoking: 60% / 57% Hypertension: 35% / 42% Diabetes: 20% / 42% High cholesterol: 35% / 57%	Two groups: 1) FFR ≥ 0.75 received no intervention. 2) FFR < 0.75 Coronary revascularisation (one stent, six, CABG).	Mortality (all cause or cardiac related). Angina	FFR ≥ 0.75 / FFR < 0.75 All cause mortality: 10% / 29% Cardiac mortality: 0% / 14% Angina: 5% / Not stated Statistical significance of these outcomes was not presented by the study investigators. However, Fisher's exact test used by the authors of this review found no significant difference in all cause mortality or cardiac mortality between the two cohorts ($P > 0.2$).	• No comparison between FFR and stress testing. • Small sample size. • Age range not presented limiting knowledge of the spectrum of patients. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. However, mortality is an objective outcome. • Four of 20 patients in FFR ≥ 0.75 group had a stent implanted in an affected artery other than the left main coronary artery. • Some discrepancy in the number of participants followed up in the FFR ≥ 0.75 group (19 described in the discussion yet there were 20 in the original group). Authors' conclusions: Results suggest the safety of deferring coronary revascularisation in patients with left main coronary artery stenosis and FFR ≥ 0.75. Study emphasises the inability of the percentage of luminal stenosis to differentiate between significant and no significant stenosis.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Leesar et al., 2003) Level II USA	RCT: FFR versus stress testing. Inclusion criteria: Patients with unstable angina or non-ST-segment elevation MI (NSTEMI). Enrolled if episode of angina of > 20 minutes duration or recurrent episodes of angina at rest and at least one of: - new ST depression - transient ST elevation - new T wave inversion in ≥ 2 leads - elevated cardiac markers - history MI - prior coronary artery disease or history of PCI. Only enrolled if a single lesion of intermediate severity was identified on coronary angiography. Exclusion criteria: Incessant chest pain not responding to medical therapy. Left main or multivessel CAD. Prior CABG. Vessels totally occluded or supplying an akinetic territory. Recruitment: Aug 1999 to March 2001. WaveWire used to measure FFR. IC Adenosine 36-42 μg in left coronary artery, 18-24 μg in right.	Total 70 participants (35 received stress myocardial perfusion imaging and 35 received FFR measurement). Stress Testing / FFR Mean age 55 years / 59 years Male 63% / 69% Ejection fraction 53% / 50% Tobacco abuse 43% / 57% Hypertension 74% / 71% Diabetes mellitus 31% / 37% Hyperlipidaemia 63% / 54%	Two groups: 1) Stress perfusion scintigraphy. 2) FFR group. FFR ≥ 0.75 or negative stress test – no intervention. FFR < 0.75 or positive stress test – PCI.	Mortality (all cause and cardiac related). MI CABG PTCA Readmission for unstable angina.	FFR (%) / Stress testing (%) All cause mortality 0 / 0 Cardiac mortality 0 / 0 MI 3 / 3 CABG 6 / 3 PTCA 0 / 0 Readmission for unstable angina 14 / 17 No significant differences in outcomes.	• Comparison between FFR and stress testing. • Age range not presented, limiting knowledge of the spectrum of patients. • Small sample size limiting power to detect a significant difference in outcome between testing procedures. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. • All received assigned intervention. • 97% follow-up in both groups (mean 14 months follow-up in FFR group and 12 months stress test group). • Method of randomisation unclear. • Note limited eligibility criteria. Authors' conclusions: A decision-making strategy based on FFR appears to be superior to one based on stress testing in patients with unstable angina. This needs to be further tested in a large, multi-centre, prospective, randomised trial.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Lopez-Palop et al., 2004) Level III-2 Spain	Cohort study with one-year follow-up. Consecutive patients with 40-70% diameter stenosis in stent or 5mm adjacent to either of the two edges of the stent. Exclusion criteria: Angiographic study scheduled in an investigational procedure. In stent restenosis lesions in vessels with > 40% stenosis in a segment proximal or distal to the zone where the in-stent restenosis was located. Recruitment: Jan 2000 to July 2002. Radi pressure wire and WaveWire used to measure FFR. IC adenosine ≥ 100 µg bolus for hyperemia.	Total 62 participants ((40 with FFR ≥ 0.75, 22 with FFR < 0.75). FFR ≥ 0.75 FFR < 0.75 Mean age 60 years 60 years Male 70% 91% Atypical chest pain 28% 14% Stable angina 18% 27% Unstable angina 45% 55% Non-ST elevation MI 5% 0% Silent ischaemia 5% 5% Current smoker 33% 54% Hypertension 50% 54% Diabetes 50% 27% High cholesterol 63% 68%	Two groups: 1) FFR ≥ 0.75 received no intervention (followed for one year). 2) FFR < 0.75 Coronary revascularisation: 24 lesions: 9 – balloon angioplasty 7 – cutting balloon 2 – brachytherapy 5 – in stent stenting 1 - CABG	Mortality (all cause or cardiac related). MI Readmission for coronary event (angina or chest pain).	FFR ≥ 0.75 FFR < 0.75 All cause mortality 5% 0% Cardiac mortality 2.5% 0% MI 0% 14% Readmission for coronary event 23% 41% Significant difference in readmission rate between groups ($P = 0.01$). Statistical significance of difference in MI proportion between cohorts was not presented by the study investigators. However, Fisher's exact test used by the authors of this review found a marginally significant difference ($P = 0.04$).	• No comparison between FFR and stress testing. • Age range not presented, limiting knowledge of the spectrum of patients. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. • Differences in documentation of study outcome between the two groups. Authors' conclusions: Angiographic quantification of moderate in stent restenosis has a poor correlation with its functional significance as assessed by FFR. FFR should be considered as the optimum tool to decide on the necessity for re-intervention.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Meuwissen et al., 2003) Level IV The Netherlands	Case series following up patients for a mean of 318 days. Restricted to patients with FFR ≥ 0.75. Divided patients into two groups based on C reactive protein level. Single, intermediate lesion disease with non-conclusive stress test results. Exclusion criteria: Severe renal/ valvular disease. Previous CABG. MI within six weeks. Collateral vascular development. Recent (< 2 weeks) infection and/or presence of chronic inflammatory disease. Radi pressure wire. IC Adenosine 20-40 μg.	71 participants. Average age Not stated Age range Not stated Male 80% Smoking 30% Hypertension 30% Diabetes 17% Hyperlipidaemia 62% Family history of heart disease 48%	Case series of patients with FFR ≥ 0.75.	Cardiac related mortality. MI CABG PTCA	Cardiac mortality 0% MI 0% CABG 1% PTCA 7%	• No comparison between FFR and stress testing. • No comparison between FFR ≥ 0.75 and FFR < 0.75 (restricted to FFR ≥ 0.75). Therefore of very limited usefulness when considering impact of FFR measurement on outcome. • Primary interest was with the use of CRP in stratifying patients. • Variation in number of FFR measurements (measured 2-3 times with the mean used for analysis). Authors' conclusions: Conclusions related to CRP testing. Low values of CRP were associated with an almost event-free survival.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Ozdemir et al., 2002) Level IV Turkey	Followed patients with FFR ≥ 0.75 to MI or death. Mean follow-up 16.6 months (minimum 6 months follow up). Patients with intermediate coronary stenoses (30-70% diameter stenosis by quantitative coronary angiography). FFR ≥ 0.75 in at least one major epicardial coronary artery. Recruitment: June 1999 to Dec 2000. Radi pressure wire used (mean of two measurements). IC Adenosine (30 μg for left coronary artery, 20 μg for right).	51 participants. Mean age 54 years Age range 31-72 Male 82% Atypical angina 19% Typical stable angina CCS class 1 2% CCS class 2 27% CCS class 3 8% Unstable angina 18% Post MI 14% Positive stress test 12% Ejection Fraction 63% Hypertension 41% Diabetes mellitus 16%	No specific intervention.	Mortality (all cause or cardiac). MI Target vessel revascularisation.	All cause mortality 0% Cardiac related mortality 0% MI 0% Target vessel Revascularisation 6% Twenty lesions with perfusion defects on thallium scan – three had a cardiac event during follow-up.	• No comparison between FFR and stress testing. • Appropriate spectrum of patients. • No comparison between FFR ≥ 0.75 and FFR < 0.75 (restricted to FFR ≥ 0.75). Therefore of very limited usefulness when considering impact of FFR measurement on outcome. • Unclear if consecutive patients were used. • Level of follow-up not stated. • Lesions in other coronary arteries with stenosis >70% were revascularised (n=18, 35% of sample). • Only 20 of the 51 participants had a stress test. Authors' conclusions: The absence of thallium scan results in 40% of the lesions means it is not possible to come to a firm conclusion about the value of perfusion scan data to predict the clinical behaviour of intermediate coronary stenoses.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Pijls et al., 1996) Level III-2 NHMRC Level II susceptibility to bias criteria The Netherlands and Belgium	Comparison of FFR and the "triple stress test" (bicycle exercise test, thallium scintigraphy and dobutamine stress echocardiography). Results of FFR pre-intervention compared with "triple stress test" with FFR < 0.75 then proceeding to revascularisation. Inclusion criteria: Chest pain. Angiographically detectable stenosis of moderate severity (~50%) in proximal part of one major coronary artery. Normal LV function. Uncertainty whether chest pain was related to reversible ischaemia caused by moderate stenosis. Radi pressure wire (0.018") used with IV adenosine 140 μg/kg/min.	Total 45 participants (24 FFR ≥ 0.75, 21 with FFR < 0.75). FFR ≥ 0.75 / FFR < 0.75 Mean age: 55 years / 54 years Age range: Not stated / Not stated Male: 54% / 71%	FFR < 0.75: coronary revascularisation.	Reference standard: "triple stress test". Ischaemic events.	Estimates of FFR validity with the "triple stress test" as the reference standard. If at least one of the three stress tests was positive evidence of ischaemia was considered to be present (ie, reference test positive). FFR cut point of 0.75: Sensitivity 87.5% (95% CI 67.6-97.3) Specificity 100% (95% CI 83.9-100) PPV 100% (95% CI 83.9-100) NPV 87.5% (95% CI 67.6-97.3) LR+ ∞ LR- 0.13 (95% CI 0.04-0.36) Group with FFR ≥ 0.75 Ischaemic events at mean 14 months follow-up: 0%	• No comparison between FFR and stress testing. • Imperfect reference standard. • Lack of risk factor data limiting knowledge concerning spectrum of patients. • Blinding status unclear. • Clinical data available at time of performing tests unclear. • No verification bias. • Large size pressure wire used (0.014" is now routine compared with the 0.018" used in this study). • FFR also measured following intervention but the cut point used was 0.75 so was markedly different to the cut off recommended in current use (at least 0.90). Authors' conclusions: Measuring FFR during coronary arteriography is useful in determining whether an angiographically moderate stenosis is functionally important and may therefore be responsible for reversible myocardial ischaemia.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Reczuch et al., 2004) Level III-2 Poland	Cohort study with mean follow-up of 15 months. Patients with stable angina and borderline lesions (reduction in diameter by 50-70% visually) in ≥ 2 epicardial arteries. Exclusion criteria: Acute coronary syndrome during the six months preceding the study. Heart failure or LVEF < 50%. Coronary lesions localised in vessels with diameter < 2.5mm. Two lesions in same vessel. Presence of aorto-coronary lesions. WaveWire was used to measure FFR. IC adenosine 30 or 60 µg bolus for hyperemia.	Total 16 participants. Average age 60 years Male 69% Smoking (current) 19% Hypertension 75% Diabetes, type 2 25% Past history of MI 44%	Two groups: 1) FFR > 0.75 received no intervention (followed for one year). 2) FFR < 0.75 PCI: Four of eight received a stent.	Reintervention (CABG or PTCA).	FFR > 0.75 FFR < 0.75 CABG or PTCA 8% of lesions 13% of lesions	• No comparison between FFR and stress testing. • Age range not presented, limiting knowledge of the spectrum of patients. • Unclear if both groups were similar at baseline – potential selection bias and potential for confounding. • Small sample size. • Only single outcome measure of interest limiting usefulness of the study. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. • Unclear if consecutive patients were selected and the proportion of eligible patients who participated was not stated. • Median follow-up in no-intervention group was 15 months compared with 17 months in intervention group. • Discrepancies in results. Data based on lesions rather than patients. Authors' conclusions Decision not to perform revascularisation based on FFR measurement is associated with good clinical outcomes. Use of FFR prevents unnecessary revascularisation procedures.

Table G.2 Studies included under effectiveness for indication 1 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Rieber et al., 2002a) Level III-2 Germany	Registry-based study following patients post-stenting. Mean follow-up 10.9 months. Analysed like a case control study with cases having a cardiac event (Cardiac death, MI or coronary artery revascularisation). Inclusion criteria: Were elective stent implantation and having a final FFR measurement available. Patients with acute coronary syndromes or chronic total occlusion were excluded. Radi pressure wire or WaveWire were used in conjunction with IC Adenosine 20-40 µg.	Total of 89 participants. Average age 63 years Age range Not stated Male 74% Smoking 44% Hypertension 75% Diabetes mellitus 27% High cholesterol 78% Family history of heart disease 37%	All patients received a stent. Study examined outcome between groups with an FFR post-stenting with grouping cut point being 0.94.	Cardiac related mortality. MI Coronary artery revascularisation.	Total of 16 events: Cardiac mortality: 6% MI: 1% Revascularisation: 11% Multivariate analysis FFR<0.94 associated with risk of cardiac event: Risk ratio 3.50 (95% CI 1.29-9.52), *P* = 0.01	• Age range not presented, limiting knowledge of the spectrum of patients. • Variation in FFR cut point between studies when FFR is measured post intervention. • First event encountered in each patient was entered. • Unable to assess whether change in management would have an impact on health outcome in this study population (there was no change in management among patients with a low FFR). • Mean 1.33 stents per patient (range 1-3) • Potential confounding by type of stent. • 100% follow-up achieved. • Consecutive sampling used. • Blinding status not stated.

Table G.3 Studies included under effectiveness for indication 2

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Bech et al., 1999) Level III-2 The Netherlands and Belgium	Registry-based study with 24 months follow-up examining the impact of adequate anatomic and functional result post-PTCA. Adequate functional result: FFR ≥ 0.90 post PTCA. Adequate anatomic result: DS < 35% post PTCA. Inclusion criteria: Underwent PTCA in 1994. Normal LV function. Positive exercise test within 24 hours before PTCA. Radi pressure wire used with IV Adenosine 140 µg/kg/min for 2-4 minutes.	Total 58 participants. Adverse event occurred / No adverse event Average age: 63 years / 60 years Age range: Not stated / Not stated Male: 88% / 62% Smoking: 19% / 26% Hypertension: 31% / 33% Diabetes: 13% / 19% High cholesterol: 19% / 36% Family history of heart disease: 31% / 45%	No specific intervention. Specifically, management was not changed as a result of the FFR result.	All cause mortality. MI Unstable angina. Coronary artery revascularisation.	Event-free survival with optimal anatomic and functional result versus either or both suboptimal anatomical and suboptimal functional result (24 months): 88% versus 59% ($P = 0.01$) If FFR was used alone "an almost similar event free survival was observed". Multivariate analysis. FFR associated with risk of adverse event ($P < 0.01$)	• No FFR/ stress test comparison. • Age range not presented limiting knowledge of the spectrum of patients. • Blinding status unclear. • 100% follow-up at 24 months. • 58 of 60 eligibles participated (97%). Two were excluded as they progressed directly to CABG when PTCA was unsuccessful. • 1994 was chosen as the study year to avoid bias by studying an unstented population from a more recent time. • Unable to assess whether change in management would have an impact on health outcome in this study population (there was no change in management among patients with a low FFR). • Variation in FFR cut off used across studies when applying post-intervention. Authors' conclusions: A subgroup of approximately 45% of patients can be identified in whom outcome is excellent after PTCA, even without stenting. Those patients can be identified by measuring coronary pressure after PTCA and establishing an FFR ≥ 0.90.

Table G.3 Studies included under effectiveness for indication 2 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Muramatsu et al., 2002) Level III-2 Japan	Cohort study based on FFR level after PTCA. Patients restricted to those with recent MI who had adequate wave patterns when using the pressure wire. Recruitment: Jan 1998 – Dec 1998. WaveWire used. Medication to achieve maximal hyperemia was not stated.	Total of 155 participants (37 with FFR ≥ 0.94, 40 with FFR < 0.94 following PTCA, 78 in control group where FFR was not measured). FFR Measured / Control group Average age: 62 years / 64 years Age range: Not stated / Not stated Male: 79% / 73% Smoking (current): 29% / 36% Diabetes mellitus: 16% / 19% Hyperlipidaemia: 23% / 26% Left anterior descending disease: 62% / 40%	Three groups: 1) FFR ≥ 0.94. No further treatment given. 2) FFR < 0.94. Stent inserted. 3) Directly stented without measuring FFR (control group).	Survival at 700 days.	FFR group (%) / Control group (%) 700 days survival: 90% / 89% No significant difference in survival.	• No comparison between FFR and stress testing. • Age range not presented, limiting knowledge of the spectrum of patients. • Baseline differences between study groups with significantly more participants in the FFR groups having left anterior descending disease. • Blinding status unclear. • 97% follow-up at 700 days. • Non consecutive patients. • Non uniformity in stent used – multilink stent used in 80% of the FFR group and 68% of the control group. • Low power to detect difference in survival.

Table G.3 Studies included under effectiveness for indication 2 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Pijls et al., 2002b) Level III-2 USA (five centres) Europe (five centres) Asia (five centres)	Registry study analysed like a case control study at six months of follow-up. Explored relationship between post stent FFR and clinical events. Enrolled in registry if undergoing coronary stenting and a pressure wire was used. Pressure wire was used if an intermediate lesion was present or if multiple stenoses were present. No exclusion criteria. Recruitment: Jan 2000 to April 2001. Radi pressure wire used. Maximal hyperemia achieved using IC Adenosine or IC ATP or IV Adenosine or IV ATP or IC papaverine.	744 Participants (668 had no events, 76 with at least one event). No events / Events Average age: 62 years / 60 years Age range: Not stated / Not stated Male: Not stated / Not stated Smoking: 47% / 55% Hypertension: 50% / 56% Diabetes: 23% / 32% High cholesterol: 60% / 70% Family history of heart disease: 39% / 34%	FFR measured post stenting.	All cause mortality. MI PCI CABG	FFR post stenting / Any event (%) 0.75-0.80: 29.5 0.81-0.85: 22.2 0.86-0.90: 16.2 0.91-0.95: 6.2 0.96-1.00: 4.9 Multivariate analysis found two independent predictors of outcome: FFR category ($P < 0.001$) Length of stent ($P < 0.01$)	• Unable to assess the impact of change in management on health outcome in this study population (unclear if additional interventions would have reduced adverse outcomes in the participants with low FFR values post-stenting). • Age range and gender not presented limiting knowledge of the spectrum of patients. • Blinding status not stated. • Overall follow-up at 6 months 99.2%. • First event for patient counted. • Nested case control design. • Potential selection bias due to selection of patients with favourable prognosis (less plaque burden). • Unable to measure FFR post stenting in five patients. Authors' conclusions: Coronary pressure measurement is an easy, rapid and relatively cheap method to evaluate stent implantation and to predict occurrence of adverse events within six months of follow-up.

Table G.3 Studies included under effectiveness for indication 2 (continued)

Source Level Country	Study design	Sample	Interventions	Outcomes	Results	Comments
(Rieber et al., 2002b) Level III-2 Germany	Cohort study with one-year follow-up. Inclusion criteria: Referred for diagnostic coronary angiography for suspected CAD. Target lesion 50-75% diameter stenosis. Negative, inconclusive or missing stress test. Target lesion suitable for PCI. Patients with multi-vessel disease provided there was no other lesion suitable for PCI beyond the target vessel. Exclusion criteria: Significant left main disease. Acute coronary syndromes. Radi pressure wire or WaveWire were used in conjunction with IC Adenosine 120 µg.	Total 97 participants. FFR ≥ 0.75 FFR < 0.75 Average age 65 years 65 years Age range Not stated Not stated Male 73% 73% Ejection fraction 61% 61% Current smoker 9% 15% Hypertension 69% 83% Diabetes mellitus 15% 15% High cholesterol 75% 87% Past history of MI 41% 44%	Two groups: 1) FFR ≥ 0.75 received no intervention (followed for one year). 2) FFR < 0.75 PCI.	Mortality (all cause and cardiac related). MI Coronary artery revascularisation.	FFR ≥ 0.75 FFR < 0.75 All cause mortality 0% 12.5% Event-free survival (12 months) 89% 58% Significant difference in event -free survival (P = 0.001) Significant difference in all cause mortality (P = 0.01)	• No FFR/ stress test comparison. • Age range not presented. • Unclear if consecutive patients were used. • Participants were not blind to intervention status and unclear if outcomes were measured blind to intervention status. • Not stated if any of the non-intervention group received PCI or if any of the intervention group did not receive PCI. • 96% follow-up at 12 months. • 37 of 48 (77%) in the PCI group received a stent. • Potential confounding with more complex lesions in the intervention group. • Potential underestimation of adverse events due to missing silent MIs. • 23 of the FFR < 0.75 group had non-pathologic or non-diagnostic stress tests indicating useful data from FFR. Authors' conclusions: Deferring patients from PCI if FFR is not critically reduced is a safe option even in patients with multi-vessel disease and complex coronary lesions.

Abbreviations

Δ	change in
95% CI	95 per cent confidence interval
ATP	adenosine – 5' - triphosphate
AV	atrio-ventricular
BP	blood pressure
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCS	Canadian Classification Society
CFR	coronary flow reserve
CHD	coronary heart disease
CRP	C Reactive Protein
DARE	Database of Abstracts of Reviews of Effectiveness
DS	diameter stenosis
ECG	electrocardiogram
EF	ejection fraction
FFR	fractional flow reserve
Fr	French
HTA	Health Technology Assessment
IC	intracoronary
IV	intravenous
IVUS	intravascular ultrasound
KM	Kaplan Meier

LCA	left coronary artery
LV	left ventricular
MI	myocardial infarction
MSAC	Medicare Services Advisory Committee
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NSTEMI	non-ST-segment elevation MI
PCI	percutaneous coronary intervention
P.Hx	past history
PTCA	percutaneous transluminal coronary angiography
RCA	right coronary artery
RCT	randomised controlled trial
SPECT	single photon emission computed tomography
Tc	technetium

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