NICE advice

The PressureWire fractional flow reserve measurement system for coronary artery disease

Medtech innovation briefing
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Summary

Effectiveness	Adverse events and safety
• Evidence comes from 3 large multicentre randomised controlled trials, 1 single centre randomised controlled trial and 1 large register. • Three systematic reviews, 4 randomised controlled trials and 1 large cohort study indicate that the PressureWire devices can be effective as adjuncts to coronary angiography to identify functionally significant stenosis. • In patients with stable coronary artery disease and fractional flow reserve (FFR) of less than 0.8, outcomes were better for FFR-guided percutaneous coronary intervention (PCI) than for medical treatment alone.	• An FFR-guided strategy, compared with an angiography-guided approach, resulted in no statistically significant difference in relative risk reduction for major adverse cardiac event outcomes. • In 1 randomised controlled trial, major adverse cardiac events were significantly improved by FFR-guided PCI at 1 year, but the difference was not significant at 2 years. There were significantly fewer myocardial infarction events in the FFR-guided PCI group at 2 years than in the angiography group.

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Costs and resource use	Technical factors
• The PressureWire Aeris costs £598.80 and PressureWire Certus (with Agile tip) costs £499. Each PressureWire FFR device is single use. • Four economic analyses evaluated FFR guided-strategies using the PressureWire FFR devices, but no published economic analyses based in the UK were identified.	• PressureWire FFR devices are used by interventional cardiologists in a cardiac catheterisation laboratory setting. • The PressureWire Certus device is used with the Quantien proprietary monitor unit (St Jude Medical), purchased separately; the PressureWire Aeris device uses wireless transmission to a receiver unit connected to monitoring platforms with FFR capability.

Key points

The PressureWire Aeris and PressureWire Certus (with Agile Tip) fractional flow reserve (FFR) devices are intended to measure the functional stenosis in a coronary artery, to help with treatment decisions in coronary artery disease and evaluate effectiveness of treatment. The PressureWire FFR devices have been compared against coronary angiography in clinical studies.

Evidence from 3 systematic reviews, 4 randomised controlled trials and 1 large cohort study indicates the PressureWire devices can be effective as adjuncts to coronary angiography to identify functionally significant stenosis, to help determine the best treatment for people with coronary artery disease.

Four economic analyses evaluated FFR guided-strategies using the PressureWire FFR devices. However, they did not directly address whether using the devices would be cost effective in the NHS.

Introduction

Coronary heart disease causes around 94,000 deaths each year in the UK (Ludman 2013a,b). Atherosclerosis is a disease process in which fat accumulates in the coronary arteries leading to fatty plaques that are visible on angiogram.

Stable angina occurs when the blood flow to the heart is restricted by a narrowing of the coronary arteries. It causes chest pain after physical exercise or stress. There is a risk that it may lead to acute coronary syndrome, including unstable angina and myocardial infarction. In myocardial

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infarction the blood flow in a coronary artery is blocked for long enough that the heart muscle it supplies starts to die. In ST elevation myocardial infarction (STEMI), the vessel remains blocked, whereas in non-ST elevation myocardial infarction (NSTEMI) flow is spontaneously re-established so that ST elevation does not occur. The pathology for the 2 syndromes is the same but STEMI needs to be treated more urgently. Unstable angina is new onset angina (usually within 24 hours) or abrupt deterioration in previously stable angina, often occurring at rest.

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

CE marking

Two PressureWire fractional flow reserve (FFR) devices (St Jude Medical) are currently available: PressureWire Aeris and PressureWire Certus (with Agile Tip). Both are class III medical devices and received CE marking in 2009 and 2012 respectively.

Intended use

The PressureWire FFR devices measure FFR, a physiological parameter used to assess the severity of stenoses in the coronary arteries. This briefing describes the use of PressureWire FFR devices in the investigation of stenoses in coronary arteries. In this context they are designed to determine whether a stenosis detected during angiography is functionally significant (that is, causes ischaemia). FFR can potentially inform the decision about whether to perform revascularisation, and on which lesions, or manage the symptoms conservatively with medical therapy.

The PressureWire FFR devices may also be used in assessing blood flow after stent placement and in investigating renal arteries. These uses are within the intended use of the device and covered by the CE mark, but are outside the scope of this briefing.

Setting and intended user

The PressureWire FFR devices are used by interventional cardiologists in a cardiac catheterisation laboratory setting, during diagnostic angiography or percutaneous coronary interventions (PCI).

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Description

Angiography is an X-ray based imaging technique that uses a contrast agent to visualise narrowing (stenosis) in the coronary arteries that may be responsible for cardiac ischaemia. Angiography uses a percutaneous catheter introduced to the coronary arteries via a peripheral artery (femoral or radial), and guided by a guidewire.

PCI involves treating coronary artery narrowing by balloon angioplasty, with or without the use of a stent, under angiography. Coronary artery bypass grafting (CABG) may be necessary in severe cases.

The PressureWire Certus (with Agile tip) and Aeris devices are guidewires with a diameter of 0.014 inch and a sensor element at the tip. The Certus device is used with the Quantien proprietary monitor unit (St Jude Medical), purchased separately, whereas the Aeris uses wireless transmission to a receiver unit connected to monitoring platforms with FFR capability.

During PCI, the PressureWire FFR device and catheter are moved through the arterial system. The PressureWire FFR device can then be directed until the sensor tip is distal to the lesion of interest, recording arterial pressures both proximal and distal to the stenosis, enabling the FFR to be calculated.

The measurement takes place under artificially induced conditions of maximal blood flow (hyperaemia). This is usually achieved by injection of a drug such as adenosine. Under these conditions coronary blood pressure is proportional to blood flow, and the ratio of pressure before and after the stenosis is equivalent to the ratio of flow. FFR is defined as the distal coronary artery pressure divided by the proximal coronary artery pressure.

Lesions with an FFR of 0.80 or less are indicated for revascularisation in several guidelines (Montalescot et al. 2013; Patel et al. 2012; Wijns et al. 2010). There is significant inter-operator variability in the visual assessment of coronary stenoses (Carrick et al. 2011; Hoole et al. 2011), but very severe or very mild stenoses are less uncertain. FFR measurement is typically used in determining the functional significance of intermediate lesions (for example, 40–70% stenosis).

Current NHS options

Diagnostic angiography is currently the standard method used in the NHS if invasive investigation is needed to assess the severity of coronary artery disease. Angiography uses a catheter. A

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guidewire with FFR capability may be introduced subsequently into the catheter, or may be used for both the conventional guidewire function and pressure measurement.

NICE is aware of the following CE marked device that appears to fulfil a similar function:

- FloWire Doppler guidewire (Volcano Corporation)

Alternative investigations to determine whether to perform revascularisation include non-invasive testing, such as exercise tolerance testing, dobutamine stress echocardiography, myocardial perfusion imaging using radionuclides and magnetic resonance perfusion imaging. Intravascular ultrasound allows the true dimensions of the lesion and the composition of the vessel wall to be visualised (Dawkins et al. 2005).

Data from the British Cardiovascular Intervention Society indicate that in 2012, 13,762 FFR procedures were carried out compared with 6407 intravascular ultrasound procedures (during both diagnostic angiography and PCI; Ludman 2013a).

Costs and use of the technology

Each PressureWire FFR device is single use. A Quantien monitor (St Jude Medical) is also needed to use the PressureWire Certus (with Agile tip). The PressureWire Aeris device can also be used with a Quantien monitor (which includes the wireless receiver unit), or the receiver unit can be bought separately to allow the use of another monitoring platform with FFR capability. The monitors and receiver units can be used more than once.

The list prices of the PressureWire FFR devices, excluding VAT, are:

- PressureWire Aeris – £598.80
- Aeris receiver unit – £399 (only necessary if the Quantien monitor is not purchased)
- PressureWire Certus (with Agile tip) – £499
- Quantien monitor – £22,500
- 1 year full service contract – £1000
- 2 year service contract – £1499.99.

Cables to connect to the catheterisation laboratory monitors are likely to cost from £100 to £300 each depending on the system used.

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Maximal hyperaemia is needed to correctly measure FFR. This is most often achieved by giving adenosine intravenously or by intracoronary bolus. The measurement of FFR takes an extra 5–20 minutes during the angiography and there is a significant degree of technical skill and knowledge needed to ensure that pressure measurements from both the PressureWire FFR device and catheter are accurate. However, these should be within the standard competencies of an experienced interventional cardiologist.

Likely place in therapy

FFR is used for diagnostic testing and to guide treatment decisions.

The NICE clinical guideline on stable angina (NICE clinical guideline 126) states that patients should normally be treated medically. However, for people whose symptoms are not satisfactorily controlled with optimal medical treatment, coronary angiography to guide treatment strategy should be considered. Treatments may include revascularisation by PCI or coronary artery bypass surgery (CABG). The guideline states 'Additional non-invasive or invasive functional testing may be required to evaluate angiographic findings and guide treatment decisions'.

A 2011 study abstract reported that, in a UK regional cardiology centre, the indication for FFR measurement in people with NSTEMI was an 'intermediate coronary lesion (that is, 40– 80% stenosis severity) associated with diagnostic and treatment uncertainty' (Carrick et al. 2013).

The European Society of Cardiology guideline on the management of stable coronary artery disease indicates that 'FFR is recommended to identify hemodynamically relevant coronary lesion(s) when evidence of ischaemia is not available' and 'revascularization of stenoses with FFR <0.80 is recommended in patients with angina symptoms or a positive stress test' (Montalescot et al. 2013).

The American College of Cardiology issued guidelines in 2012 indicating the different situations in which using FFR for assessing lesion severity was appropriate, and the level of certainty. It also indicated that 'in patients without previous non-invasive imaging, or patients in whom the prior testing is not in concordance with the symptoms or angiographic findings.....for lesions between 50% to 69%, invasive FFR is the test preferred for diagnostic purposes' (Patel et al. 2012; Patel 2013).

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Specialist commentator comments

Measurement of FFR is already part of the pathway in some centres for people referred for PCI, when there is uncertainty about the significance of stenosis from non-invasive imaging. It is estimated that 10–18% of people referred for PCI currently have FFR measured. There is agreement that it could be used more widely, including in different settings such as diagnostic-only cardiac catheterisation laboratories in addition to those capable of performing PCI, and as a decision tool for people referred for CABG, for whom PCI may be suitable.

Barriers for wider use are the cost per use, additional time per procedure, a perceived or actual lack of expertise, and whether cardiac catheterisation laboratories can be organised to perform FFR measurement.

Evidence review

Clinical and technical evidence

Regulatory bodies

The Medicines and Healthcare products Regulatory Agency (MHRA) website reports 1 product recall notice issued on 16 September 2011. The alert advised users that a specific batch of PressureWire Aeris could produce erroneously low fractional flow reserve (FFR) values because of a production fault, and that this batch should not be used.

The USA Food and Drugs Authority (FDA) database, Manufacturer and User Device Facility Experience (MAUDE) reports 54 relevant records. Records in MAUDE are entered from a variety of sources, may contain duplicates and the accuracy has not been verified. Where details were available they included incidents of the wire or tip of the device breaking during use, and dissection or perforation during the procedure. No search was made for information on other guidewire devices.

Systematic reviews

Three systematic reviews in English were identified: Raman et al. (2013), Blue Cross and Blue Shield (2011) and Medical Services Advisory Committee (MSAC, 2005). A further systematic review, Siebert et al. (2008) was excluded as the full text was available only in German. A list of the papers included in each is in table 8. Note that the systematic reviews did not select for named devices and therefore may include data relating to FFR devices other than PressureWire FFR devices.

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Raman et al. (2013)

This peer-reviewed comparative effectiveness review was carried out for the Agency for Healthcare Research and Quality (AHRQ) in the USA (Raman et al. 2013). It focused on 5 questions, the first of which was the impact of using an intravascular diagnostic technique with angiography versus angiography alone to make therapeutic decisions, and subsequent intermediate outcomes and patient-centred outcomes. The other questions looked at were not relevant to this briefing.

Evidence included 1 randomised controlled trial (FAME) and 2 non-randomised studies (Muramatsu et al. 2002; Wongpraparut et al. 2005). The DEFER trial was excluded because it 'examined appropriateness of stenting a functionally non-significant stenosis, and did not compare FFR-guided stenting versus stenting guided by angiography alone'. It should be noted that other systematic reviews have included this trial and it is summarised later in this briefing. The FAME II trial was excluded because 'all patients underwent FFR during angiography, and FFR-guided stenting plus optimal medical therapy was compared with optimal medical therapy only.'

The reviewers assessed the risk of bias for the included studies as: FAME: low, Wongpraparut et al. (2005): medium, and Muramatsu et al. (2002): high. Study results were summarised in narrative form only.

The report found a moderate strength of evidence favouring FFR-guided stenting decisions over stent placement decisions guided by angiography alone, in patients with intermediate coronary lesions.

Blue Cross and Blue Shield (2011)

This US assessment aimed to review and evaluate available evidence comparing outcomes following FFR-guided percutaneous coronary intervention (PCI) against PCI guided by angiography alone in patients with angina (Blue Cross and Blue Shield Association Technology Evaluation Center 2011).

Evidence included 2 randomised controlled trials (DEFER and FAME) and 4 observational studies (Chamuleau et al. 2002; Legalery et al. 2005; Lindstaedt et al. 2006; Wongpraparut et al. 2005). Excluded studies were not listed.

The authors found that trial data were consistent and that results from the small observational studies were in agreement, although with limitations inherent in observational data. They noted the use of bare metal stents and single target vessels in the DEFER trial. They also noted that there

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were large numbers of moderate severity lesions in the FAME trial, where PCI in the angiography alone arm was based on physician judgement, including any non-invasive testing.

The authors concluded that the evidence suggested that identifying stenoses is insufficient to determine if revascularisation is likely to be of benefit. For patients with angina for whom revascularisation is considered, evidence suggests that FFR-guided PCI results in better outcomes than strategy guided by angiography alone.

Medical Services Advisory Committee (MSAC, 2005)

This assessment was published by the MSAC in Australia. The scope included the measurement of FFR and coronary flow reserve for single or multi-vessel coronary artery disease, for intermediate lesions (coronary stenosis 30–70%) and post-angioplasty or stenting.

Evidence included:

- 2 randomised controlled trials (Bech et al. 2001a; Leesar et al. 2003)
- 8 non-randomised studies in patients with a range of FFR levels (Bech et al. 2001b; Botman et al. 2004; Jasti et al. 2004; Jimenez-Navarro et al. 2004; Lopez-Palop et al. 2004; Reczuch et al. 2004; Rieber et al. 2002)
- 4 non-randomised studies, in patients with FFR levels considered functionally non-significant (Bech et al. 1998; Hernandez-Garcia et al. 2001; Meuwissen et al. 2003; Ozdemir et al. 2002)
- 1 study comparing FFR to a triple stress test (Pijls et al. 1996).

DEFER (Bech et al. 2001a) is described in full in this briefing.

The report also analysed studies in subgroups.

For single-lesion disease the studies were consistent with the DEFER findings, that for patients with a FFR of 0.75 or more there was with no overall difference in major cardiac events if PCI was carried out or deferred.

For left main coronary artery disease, 3 observational studies found improvements in angina status after FFR measurement regardless of intervention, but this should be treated with caution due to the observational nature of the studies.

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For multiple lesion disease 3 observational studies were compared, but no overall conclusions were drawn.

There were no studies restricted to myocardial infarction or unstable angina. Leesar et al. (2003) studied a population with unstable angina or non ST-segment elevated myocardial infarction (NSTEMI), but the 2 groups could not be separated out.

The report's recommendations were accepted by the Australian Minister for Health and Ageing: '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'.

Randomised controlled trials

Four randomised controlled trials (10 papers) were identified. Their design is summarised in table 1 and the key findings described in following text and tables.

Table 1: Summary of randomised controlled trial protocols

Study component	Description			
	DEFER	FAME	FAME II	Dambrink (2010), Ghani (2012)
Population	Stable angina, referred for elective PCI	Multi-vessel CAD, PCI indicated	Stable CAD, eligible for PCI	STEMI, already successfully treated with PCI
Treatment before randomisation	Randomise first to PCI or defer, then FFR for all	Angiogram to assess need for PCI, then randomise to receive FFR	Angiogram to assess need for PCI then FFR for all. Randomise where FFR significant	All patients had STEMI and successful PCI for culprit lesion in previous 3 weeks
Arm 1	Significant + PCI	FFR guided PCI	Significant, PCI+medical	FFR guided PCI

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Arm 2	Not significant + defer	Angiogram guided PCI	Significant, medical	Conservative treatment
Arm 3	Not significant + PCI	N/A	Not significant, medical	N/A
What would have been standard care for these patients?	All patients would have received PCI	Patients would have received angiography guided PCI	Patients would have received angiography guided PCI	Patients would have received medical treatment
Randomisation	Yes, but method not stated	Yes, sealed envelope, blocks of 25.	Yes, stratified by site, random block sizes	Yes, computer program, no other detail given
Blinded treatment	Not stated	Not stated	No	Not stated
Blinded outcomes	Not stated, Events reviewed by independent committee	Events adjudicated by independent committee who were unaware of treatment	Events adjudicated by independent committee who were unaware of treatment	Blinded for echocardiographic and radio nuclide outcomes.
CAD, coronary artery disease; FFR, fractional flow reserve; PCI, percutaneous coronary intervention; STEMI, myocardial infarction with ST-segment elevation.				

DEFER study

This multicentre randomised controlled trial was carried out in 12 hospitals in Europe and 2 hospitals in Asia between June 1997 and December 1998 (Bech et al. 2001a; Pijls et al. 2007). The pressure wire devices used were from RADI Medical Systems, the previous manufacturer of the PressureWire devices.

The DEFER trial treatment groups, and outcomes, are described in tables 2 and 3.

Event-free survival for all patients with functionally non-significant stenosis (PERFORM plus DEFER) was 76% (p=0.03). For patients with functionally non-significant stenosis, 21% of

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PERFORM and 27% of DEFER experienced 1 or more events at 5 years. In the reference group this was 39% (p=0.03 compared with the combined PERFORM plus DEFER).

In this trial, for patients with stable chest pain and functionally non-significant stenosis (FFR≥0.75), stenting did not improve outcomes. Measuring FFR could therefore help to identify patients who would not benefit from stenting.

Table 2: Summary of the DEFER trial[a]

Study component	Description
Objectives/ hypotheses	Is PCI justified in patients with stable chest pain and a functionally non-significant coronary stenosis?
Study design	Multicentre, prospective randomised controlled trial
Setting	12 hospitals in Europe and 2 hospitals in Asia between June 1997 and December 1998 Clinical follow-up was at hospital discharge and after 1, 3, 6, 12, 24 and 60 months Patients were randomised to PCI or deferral of PCI. All patients then underwent FFR measurement. In both arms patients with FFR<0.75 received PCI, and these formed the REFERENCE group. In the performance of PCI arm, patients with FFR ≥0.75 received PCI and were labelled the PERFORM group. In the deferral of PCI arm, patients with FFR≥0.75 did not receive PCI and were labelled the DEFER group Stents were bare metal stents

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Inclusion / exclusion criteria	Inclusion criteria Referral for elective PCI of a single angiographically significant stenosis (>50%) in native coronary artery with reference diameter >2.5mm No evidence of reversible ischaemia in last 2 months Exclusion criteria Total occlusion of target artery Acute Q-wave infarction Unstable angina with transient ST-segment abnormality
Variables	Primary outcome was freedom from adverse cardiac events (MACE) after 2 years of follow-up
Statistical methods	No sample size calculation was given. Intention to treat analysis Baseline characteristics were compared using chi-square test or unpaired student t-tests Kaplan-Meier survival curves for absence of adverse cardiac events and compared by the log rank test P<0.05 was considered significant. All tests were 2-tailed
Participants	There were more men than women in the study, and statistically significantly more men in the reference group (80%) than in the FFR≥0.75 group (65% DEFER, 63% PERFORM), p<0.05. Statistically significantly more non-invasive stress tests were performed in the FFR≥0.75 group (67%) than in the reference group (53%), and statistically significantly more negative results were seen (47% DEFER, 50% PERFORM) than in the REFERENCE group (31%). Age, ejection fraction, clinical history and angina class did not show significant differences
Main results	The primary end point of event-free survival in patients at 2 years was 89% in the DEFER group, and 83% in the PERFORM group (p=0.27). Event free survival of the reference group was 78% (PERFORM p=0.31, DEFER p=0.03) Event free survival at 5 years was 79% in the DEFER group, and 71% in the PERFORM group (p=0.52). Event free survival of the reference group was 61%. (PERFORM p=0.17, DEFER not reported) Event free survival for all patients with functionally non-significant stenosis (PERFORM+DEFER) was 76% (p=0.03)

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Conclusions	For patients with stable chest pain, where FFR≥0.75, stenting did not improve outcomes

CI, confidence interval; FFR, fractional flow reserve; ITT, intention to treat; n, number of patients; PCI, percutaneous interventions; RR, relative risk.

[a] The table contains information from several papers concerning the same DEFER RCT. These are: Bech et al. (2001a, 2 year results), Pijls et al. (2007, 5 year results).

Table 3: Results of the DEFER trial[a]

	DEFER Group	PERFORM group	REFERENCE group	Analysis
Randomised	n=91	n=90	n=144	
Efficacy	n=91 1 lost at 5 year	n=90 2 lost at 5 year	n=144 10 lost at 5 year	ITT
Primary outcome: event-free survival at 2 years	89.0% (80/91)	83.3% (75/90)	78.4% (106/144)	% and numbers given as reported, but % are not as calculated from numbers. p=0.27, 95% CI −15.7% to 4.6% (DEFER:PERFORM) p=0.31 (REF:PERFOM) p=0.03 (REF:DEFER)
Selected secondary outcomes				
Event-free survival at 5 years	79% (72/91)	71% (64/90)	61% (88/144)	p=0.52 (DEFER:PERFORM) p=0.17 (REF:PERFORM) p=0.03 (REF:DEFER+PERFORM)
Cardiac death	3.3% (3/91)	2.3% (2/90)	6.0% (8/144)	
Other death	3.3% (3/91)	3.4% (3/90)	3% (4/144)	

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MI (Q wave and non Q wave)	0	6.7% (6/90)	9.0% (13/144)	
Freedom from angina	67% (61/91)	57% (51/90)	72% (104/144)	p=0.028 (REF:DEFER+PERFORM) p=0.015 (Reference:Perform)
Safety	n=91	n=90	n=144	
Total adverse events	21	30	70	Reported as 'total events after 5 years'. Patients may have had more than 1 event
Patients with ≥1 event	21% (19/91)	27% (24/90)	39% (52/144)	p=0.03 (REF:DEFER+PERFORM)
CABG	1.1% (1/91)	4.5% (4/90)	10.4% (14/144)	
TVR	8.9% (8/91)	9.1% (8/90)	13.4% (18/144)	
Non-TVR	6.7% (6/91)	6.8% (6/90)	8.2% (11/144)	% and numbers given as reported, but % are not as calculated from numbers
Other	0% (0/91)	1.1% (1/90)	1.5% (2/144)	

CABG, coronary artery bypass graft; CI, confidence interval; ITT, intention to treat; MI, myocardial infarction; n, number of patients; RR, relative risk; TVR, tricuspid valve replacement.

[a] The table contains information from several papers concerning the same DEFER randomised controlled trial. These are: Bech et al (2001a), 2 year results), Pijls et al. (2007, 5 year results).

FAME study

FAME was a multicentre randomised controlled trial across 5 medical centres in the USA and 15 in Europe between January 2006 and September 2007 (Fearon et al. 2007; Fearon et al. 2010; Pijls et al. 2010; Tonino et al. 2009). FAME compared the clinical outcomes and cost effectiveness of treatment based on measurement of FFR using the pressure wire devices from RADI Medical

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Systems (in addition to angiography) against treatment guided by angiography only, in patients with multi-vessel coronary artery disease for whom PCI was appropriate.

A summary of the trial is presented in tables 4 and 5.

The study showed that measuring FFR in patients with multi-vessel coronary artery disease having PCI with drug-eluting stents significantly reduces myocardial infarction (MI) at 2 years when compared with standard angiography-guided PCI.

Four papers were identified that reported subgroup analyses of the FAME trial (Kim et al. 2012; Nam et al. 2011; Sels et al. 2011; Tonino et al. 2010), 2 of which are relevant to this briefing. A major limitation for any subsequent analysis was that the study was designed and powered to examine the original study question only, so conclusions should be treated with caution.

Sels et al. (2011) reanalysed the trial data to determine if there was a difference in benefit of FFR guidance for PCI for patients with unstable angina or NSTEMI (n=328), compared with stable angina (n=677). The absolute risk reduction from using FFR guidance compared with angiography guidance was similar (5.1% unstable angina or NSTEMI, 3.7% stable angina, p=0.922). The authors noted that FFR measurement can be limited by microvascular obstructions that are often present with MI, but that the FAME study population was defined to minimise this issue.

Kim et al. (2012) considered the impact of sex differences on FFR-guided PCI using data from the FAME study, with 744 men and 261 women. They found that the proportion of functionally significant lesions was lower in women than in men for lesions with 50–70% stenosis (21.1% compared with 39.5% respectively, p<0.001). They also reported that the FFR-guided strategy resulted in no statistically significant difference in relative risk reduction for major adverse cardiac event (MACE) type outcomes for men and women, compared with an angiography-guided approach.

Table 4: Summary of the FAME study[a] (2 year results)

Study component	Description
Objectives / hypotheses	To compare the clinical outcomes and cost-effectiveness of treatment based on measurement of FFR in addition to angiography against treatment guided solely by angiography in patients with multi-vessel coronary artery disease for whom PCI is appropriate

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Study design	Multicentre randomised controlled trial
Setting	5 medical centres in the USA and 15 in Europe between January 2006 and September 2007 Clinical follow-up was at 1 year for primary outcomes, and at 30 days, 6 months, 2 years and 5 years for secondary outcomes The patients were assessed for PCI by using angiogram, then randomised to the FFR or angiogram arm. For the FFR-guided strategy, the clinician could only stent if FFR≤0.8. 96.9% of stents were drug-eluting stents
Inclusion / exclusion criteria	Inclusion criteria: Multi-vessel coronary artery disease (≥ 50% diameter stenosis in ≥2 major epicardial vessels) and PCI indicated. Age ≥18 years Exclusion criteria: Previous coronary bypass surgery Left main coronary disease Recent ST elevation MI (<5 days) Recent non-ST elevation MI (<5 days) if peak CK is >1000 U per litre Cardiogenic shock Extremely tortuous or calcified coronary vessels Life expectancy <2 years Pregnancy Contraindicated for placement of drug-eluting stent
Variables	Primary outcome was the rate of major adverse cardiac events at 1 year, defined as a composite of death, MI and repeat revascularisation Secondary outcomes measured at 30 days, 6 months, 2 years and 5 years

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Statistical methods	Sample size based on: 426 patients in each arm, based on alpha level 0.05, statistical power of 0.8 assuming adverse cardiac events at 1 year of 14% for angiography and 8% for FFR. Intention to treat analysis Categorical variables compared using chi-square test, continuous variables compared with unpaired t-test or Mann-Whitney U test. Kaplan-Meier curves for time-to-event distribution of primary end point
Participants	Baseline characteristics of the 2 groups are reported as similar, as were the number of indicated lesions and angiographic extent and severity of CAD. In both groups there were more men than women (angiography 73% male; FFR 75% male)
Main results	The primary outcome, MACE at 1 year, occurred in 91 patients (18.3%) in the angiography-guided group, and 62 patients (13.2%) in the FFR group (P=0.02) MACE at 2 years occurred in 111 patients (22.4%) in the angiography-guided group, and 91 patients (17.9%) in the FFR group (p=0.08)
Conclusions	The primary outcome (MACE) was significantly improved by FFR-guided PCI at 1 year, but the difference was not significant at 2 years. There were significantly fewer MI events in the FFR-guided PCI group at 2 years than in the angiography group
CI, confidence interval; ITT, intention to treat; MACE, major adverse cardiac event; MI, myocardial infarction; n, number of patients; PCI, percutaneous coronary intervention; RR, relative risk. [a] The table contains information from several papers concerning the same FAME RCT. These are: Fearon et al. (2007, study design, Tonino et al. (2009, 1 year results), Pijls et al. (2010, 2 year results).	

Table 5: Results of the FAME study[a] (2 year results)

	Angiography	FFR	Analysis
Randomised	n=496	n=509	
Efficacy At 1 year At 2 years	n=496 11 lost 36 lost	n=509 8 lost 29 lost	ITT p=0.45 p=0.31

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Efficacy	n=496 36 lost	n=509 29 lost	ITT p=0.31
Primary outcome: MACE at 1 year	18.3% (91/496)	13.2% (62/509)	p=0.02, RR=0.72 95% CI 0.54–0.96
MACE at 2 years	22.4% (111/496)	17.9% (91/509)	p=0.08, RR=0.8 95% CI 0.62–1.02
Selected secondary outcomes			All outcomes were at 2 years, unless stated
All-cause mortality	3.8% (19/496)	2.6% (13/509)	p=0.25 RR=0.67 95% CI 0.33–1.34
MI	9.9% (49/496)	6.1% (31/509)	p=0.03 RR=0.62 95% CI 0.40–0.95
CABG or repeat PCI	12.7% (63/496)	10.6% (54/509)	p=0.3 RR=0.84 95% CI 0.59–1.18
Periprocedural infarctions (from 1 year results paper)	3.2% (16/496)	2.4% (12/509)	Not stated
Patients without event and free from angina	64.8% (284)	68.2% (315)	p=0.29 Patients without information on angina status excluded, denominator not given
EQ5D score at 1 year	73.7±16.0	74.5±15.7	p=0.65 Not reported at 2 years

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Total drug-eluting stents used	1,359	980	p<0.001
Safety	n=496	n=509	Intention to treat analysis
Total adverse events	28.6% (142/496)	20.8% (106/509)	Reported as 'total events'. This includes MACE, but additional events were not reported in detail. Some patients may have more than one event

CI, confidence interval; EQ5D, EuroQol-5D quality of life measure, ITT, intention to treat; MACE, major adverse cardiac events; n, number of patients; RR, relative risk.

[a] The table contains information from several papers concerning the same FAME RCT. These are: Fearon et al. (2007, study design), Tonino et al. (2009, 1 year results), Pijls et al. (2010, 2 year results).

FAME II study

The FAME II multicentre randomised controlled trial was conducted in 28 sites in Europe and North America and enrolled 1220 patients (De Bruyne et al. 2012; Fearon et al. 2013). Recruitment was from May 2010 to January 2012, at which point the trial was stopped because of a highly significant difference in the primary end point between the groups. The objective was to determine whether FFR-guided PCI, using either PressureWire Aeris or PressureWire Certus (with Agile Tip), with drug-eluting stents plus the best available medical therapy was superior to the best available medical therapy alone in reducing adverse cardiac events in patients with stable coronary artery disease.

For patients with functionally significant stenosis, the trial showed those who received PCI had statistically significantly fewer MACE events than those who received medical treatment only. There was no significant difference for these patients in occurrence of death or MI, but there were statistically significantly more urgent revascularisations for patients with functionally significant stenosis who were treated medically rather than receiving PCI. As the study was powered to detect a difference in MACE, non-significant results in the component outcomes may be inconclusive. The difference in urgent revascularisations may have been influenced by healthcare professionals being more likely to recommend PCI for patients who have only received medical treatment to date (Boden 2012).

A summary of the trial is presented in tables 6 and 7.

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The patients in this trial were already being considered for PCI, and had at least 1 vessel with 50% or greater stenosis, assessed by angiography. They were randomised to medical treatment or PCI if functionally significant stenosis was identified using FFR measurement. It was not clear how many would have received PCI if not enrolled in the trial.

If normal treatment for this group of patients would have been to give best available medical treatment, FFR measurement could have helped to identify patients who would have benefitted from treatment with PCI.

If normal treatment would have been PCI, then FFR measurement would have helped to identify patients for whom PCI did not provide a benefit in this trial. Outcomes for patients without functionally significant stenosis, treated medically, were not statistically significantly different from outcomes for patients with functionally significant stenosis who received PCI.

Table 6: Summary of the FAME II trial (De Bruyne et al. 2012)

Study component	Description
Objectives / hypotheses	To determine whether FFR-guided PCI with drug-eluting stents plus the best available medical therapy is superior to the best available medical therapy alone in reducing adverse cardiac events in patients with stable coronary artery disease
Study design	Multicentre randomised controlled trial
Setting	28 sites in Europe and North America, with 1220 patients. Recruitment was from May 15 2010 to January 15 2012 at which point the trial was stopped due to a highly significant difference in the primary end point between the PCI and medical therapy groups. All patients underwent FFR. Where FFR>0.8 lesions were included in a register, and 166 were randomly selected for follow-up. Where FFR≤0.8, patients were randomised to PCI and medical treatment, or to medical treatment alone

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Inclusion/ exclusion criteria	Inclusion criteria: Stable angina, or atypical / no chest pain but documented ischaemia on non-invasive testing At least one stenosis ≥50% in native coronary artery with diameter ≥2.5mm, supplying viable myocardium Eligible for PCI Exclusion criteria: Preferred treatment is CABG Left main coronary artery disease needing revascularisation Patients with a recent STEMI or non-STEMI (<1 week) Prior CABG, contraindicated to dual anti-platelet therapy LVEF<30%, Severe left ventricular hypertrophy, Planned valve or aortic surgery, tortuous/calcified coronary arteries Life expectancy <2 years, age <21, pregnancy
Variables	Composite of death from any cause, non-fatal MI or unplanned urgent revascularisation (MACE) at 2 years.
Statistical methods	Sample size of 816 in each group was calculated to provide 84% power to detect a relative risk reduction with PCI of 30% for the primary end point at 24 months, alpha=0.05. Intention to treat analysis Mantel-Cox to calculate hazard ratios and 95% CI Log rank test for p values Kaplan Meier curves for primary end point. Landmark analyses for events at landmark point of 7 days
Participants	There were more men than women in the trial (coronary +medical treatment 79.6%, medical therapy 76.6%, registry 68.1%). There were significantly less men in the registry group than in the combined randomised groups, p=0.005 There was less peripheral vascular disease in the registry group than in the combined randomised groups (PCI+medical treatment 9.6%, medical therapy 10.7%, registry group 4.8%), p=0.03, and fewer lesions per patient (PCI+medical treatment 1.87±1.05, medical therapy 1.73±0.94, registry group 1.32±0.59), p<0.001

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Main results	For the primary end point at 2 years, there was a significant difference between the medical treatment group (12.7%) and the registry group (3.0%), p=0.001, and also between the PCI+medical treatment group (4.3%) and the medical treatment only group (12.7%), p<0.001. The difference between the PCI+medical treatment group and the registry group was not significant, p=0.61. There was a significant difference between the medical treatment only and registry groups, p=0.001
Conclusions	In patients with stable coronary artery disease and FFR≤0.8 outcomes were better for FFR-guided PCI than for medical treatment alone
CI, confidence interval; FFR, fractional flow reserve; ITT, intention to treat; LVEF, left ventricular ejection fraction; n, number of patients; PCI, percutaneous intervention; RR, relative risk.	

Table 7: Results of the FAME II trial (De Bruyne et al. 2012)

	PCI plus medical treatment	Medical treatment only	Registry	Analysis For PCI+MT:MT[a]
Randomised	n=447	n=441	n=166	
Efficacy	n=447	n=441	n=166	ITT
Primary outcome: MACE at 2 years	4.3% (19/447)	12.7% (56/441)	3.0% (5/166)	p<0.001 HR=0.32 95%CI 0.19–0.53
Selected secondary outcomes:				
Death (any cause)	0.2% (1/447)	0.7% (3/441)	0% (0/166)	p=0.31 HR=0.33 95% CI 0.03–3.17
MI	3.4% (15/447)	3.2% (14/441)	1.8% (3/166)	p=0.89 HR=1.05 95% CI 0.51–2.19

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Urgent revascularisation	1.6% (7/447)	11.1% (49/441)	2.4% (4/166)	p<0.001 HR=0.13 95% CI 0.06–0.3
Safety	n=447	n=441	n=166	
Serious adverse events				The events were listed, however the categories overlap and it was not possible to deduce a total number
Any revascularisation	3.1% (14/447)	19.5% (86/441)	3.6% (6/166)	p<0.001 HR=0.14 95% CI 0.08–0.26
Stroke	0.2% (1/447)	0.5% (2/441)	0.6% (1/166)	p=0.56 HR=0.49 95% CI 0.04– 5.50
Stent thrombosis	1.1% (5/447)	0.2% (1/441)	0.6% (1/166)	p=0.10 HR=4.98 95% CI 0.59–42.25

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; n, number of patients; RR, relative risk.

[a] Additional comparisons are given in the supplementary appendix available for De Bruyne (2012).

Dambrink (2010), Ghani (2012)

This was a randomised controlled trial carried out in a single tertiary referral centre in the Netherlands. It used pressure wire devices from RADI Medical Systems, the previous manufacturer of the PressureWire devices. Patients were recruited between June 2004 and March 2007. The objective was to test the hypothesis that in patients with multi-vessel disease successfully treated with PCI for STEMI, subsequent early FFR-guided PCI would result in improved global left ventricular function and fewer cardiac events during follow-up compared with conservative treatment. The trial is summarised in tables 8 and 9.

The authors concluded that an early ischaemia-guided invasive strategy prevents later PCI procedures but does not result in a reduction in MACE at 6 months.

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After 3 years of follow-up the authors concluded that FFR-guided additional revascularisation of early FFR-guided PCI of the 'non-culprit' lesions would result in improved global left ventricular function and fewer cardiac events during follow up compared to conservative treatment. The non-culprit lesions are those that were not treated in the acute STEMI episode.

The strength of these conclusions was limited by the study finishing before recruitment finished, and by combining results (re-infarction and death) in groups that were not originally planned.

Table 8: Summary of the randomised trial reported by Dambrink et al. (2010); Ghani et al. (2012)

Study components	Description
Objectives / hypotheses	To test the hypothesis that in patients successfully treated with PCI for STEMI and with multi-vessel disease, subsequent early FFR-guided PCI would result in improved global left ventricular function and fewer cardiac events during follow-up compared to conservative treatment
Study design	Randomised controlled trial. Patients were randomised in 2:1 ratio to invasive treatment: FFR-guided revascularisation within 3 weeks of STEMI, or conservative treatment
Setting	Single tertiary referral centre in The Netherlands. Patients were recruited between June 2004 and March 2007[a].
Inclusion / exclusion criteria	Inclusion criteria: successful PCI defined by residual diameter stenosis <50% and TIMI 3 flow[b]. Multi-vessel disease was defined as 1 or more significant stenoses in at least 2 major epicardial coronary arteries, or the combination of a side branch and a main epicardial vessel provided that they supplied different territories. A significant stenosis was defined as a diameter stenosis of at least 50% in luminal diameter. The reference diameter adjacent to the lesion had to be ≥2.5 mm. Exclusion criteria: urgent indication for additional revascularisation, age >80 years, chronic occlusion of one of the non-infarct related arteries, prior CABG, left main stenosis of 50% or more, restenotic lesions in non-infarcted arteries, chronic atrial fibrillation, limited life expectancy, or other factors that made complete follow-up unlikely

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Variables	Primary outcome: Ejection fraction assessed by radionuclide ventriculography at 6 months Secondary outcomes: Change in ejection fraction (baseline to six months) Wall motion score, left ventricular end-systolic and end-diastolic volume and ejection fraction at 6 months by echocardiography MACE
Statistical methods	A 2-sided p value of <0.05 was considered statistically significant. A difference of 5% in ejection fraction was considered clinically relevant. With a standard deviation of 12%, a power of 80% and alpha of 0.05, 92 patients in both groups were needed to detect a significant difference at the p<0.05 level. A 10% drop-out rate was taken into account. It was anticipated that 50% of lesions, when assessed by FFR, would warrant revascularisation, hence the 2:1 randomisation ratio and target of 300 patients. Students t-test was used for continuous variables. Chi-square was used for proportions
Results	The study by Dambrink et al. 2010 recruited 121 patients successfully treated with PCI for STEMI and with multi-vessel disease and randomised them to either early (within 3 weeks of STEMI) FFR-guided PCI or conservative treatment. 6 month follow-up: Ejection fraction was comparable between groups (invasively treated group: 59±9% versus conservative group: 57±9%, p=0.362), and there was no difference in MACE between invasively and conservatively treated patients (21 versus 22%, p=0.929) 3-year follow-up: There was no significant difference in all-cause mortality between the invasive treatment and conservative treatment groups; 4 patients (3.4%) died in the invasive treatment group (p=0.29). Re-infarction occurred in 14 patients (11.8%) in the invasive treatment group compared with none in the conservative treatment group (p=0.002). Re-PCI was performed in 7 patients (8.9%) in the invasive treatment group and in 13 patients (32.5%) in the conservative treatment group (p=0.001). There was no difference in MACE between the 2 strategies (35.4 versus 35.0%, p=0.96

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Participants	Patients successfully treated with PCI for STEMI and with multi-vessel disease. In the invasive treatment group, PCI was performed if FFR<0.75. PCI was performed for all severe lesions (>90% stenosis). In the conservative treatment group, PCI was discouraged but if symptoms occurred, ischaemia-guided revascularisation was performed based on exercise test, dobutamine stress echocardiography or myocardial scintigraphy
Main results	The study by Dambrink et al. 2010 recruited 121 patients successfully treated with PCI for STEMI and with multi-vessel disease and randomised them to either early (within 3 weeks of STEMI) invasive FFR-guided PCI or conservative treatment. The outcome measures were global left ventricular function and cardiac events. At 6 months follow-up, there were no statistically significant differences between groups for ejection fraction or MACE, but there was a higher rate of death and MI in the invasively treated group than the conservatively treated group by ITT. At 3 years' follow-up, there were more deaths and reinfarctions in the invasively treated group compared to the conservatively treated group, but no difference between groups for MACE
Conclusions	Authors' conclusions: an early ischaemia-guided invasive strategy prevents later PCI procedures but does not result in a reduction of total major adverse cardiac events at 6 months. These findings support a conservative strategy as currently advocated by the guidelines. After 3 years of follow-up the authors concluded that FFR-guided additional revascularisation of non-culprit lesions early after primary PCI resulted in more deaths and/or re-infarctions compared with a more conservative strategy of ischaemia-guided revascularisation at a later stage
CI, confidence interval; FFR, fractional flow reserve; ITT, intention to treat; MACE, major adverse cardiac event; MI, myocardial infarction; n, number of patients; PCI, percutaneous coronary intervention; RR, relative risk; TIMI, thrombolysis in myocardial infarction. [a] The trial was stopped before the target accrual of 300 patients was reached because of slow recruitment and in clinical practice over time that could create an inhomogeneous study population. It was therefore underpowered. [b] Ghani et al. (2012) publication states a TIMI ≥2.	

Table 9: Results of the randomised controlled trial reported by Dambrink et al. (2010) and Ghani et al. (2012)

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	Invasive treatment group	Conservative treatment group	Analysis
Randomised	n=80	n=41	Randomised at 2:1 ratio because an anticipated 50% of FFR assessed lesions would warrant revascularisation
Efficacy	n=80	n=41	
Primary outcome: ejection fraction assessed by radionuclide ventriculography at 6 months	EF=58.9% ±9.4%	EF=56.9% ±9.3%	Assessed in 90/121 (74%) of all patients Difference=2%, p=0.362
Selected secondary outcomes			
Change in ejection fraction (baseline to 6 months)	-0.2±6.7%	+0.1±7%	Assessed in 90/121 (74%) of all patients No p value reported
Wall motion score index at 6 months	n=80 Index=1.20±0.20	n=41 Index=1.22±0.27	p=0.607 Measure of spread not reported (presumably a mean for a continuous variable)
End-systolic volume at 6 months	n=80 41.4±16.3	n=41 45.9±35.7	Units not reported p=0.448
End-diastolic volume at 6 months	n=80 92.7±29.5	n=41 98.9±44.1	p=0.482
Ejection fraction (echocardiographic) at 6 months	n=80 55.7±8.2	n=41 56.3±11.8	p=0.784
MACE (6 months)	21%	22%	p=0.929 ITT analysis
Death (6 months)	2.5%	0%	p=0.015 ITT analysis
MI (6 months)	14%	0%	p=0.015 ITT analysis

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PCI (6 months)	13%	22%	p=NS ITT analysis
CABG (6 months)	6.3%	0%	p=NS ITT analysis
Non-culprit-related PCI	n=65[a] Rate=6%	n=40 Rate=22%	p=0.017 Per protocol analysis[a]
Non culprit related MACE	16%	22%	
Death and MI (6 months)	n=65[a] Rate=9%	n=40 Rate=0%	p=0.079 Per protocol analysis[a]
MACE (6 months)	n=65[a] 14%	n=40 22%	p=0.295 Per protocol analysis[a]
Death (6 months)	n=65[a] 3%	n=40 0%	p=0.079 Per protocol analysis[a]
MI (6 months)	n=65[a] 9%	n=40 0%	p=0.079 Per protocol analysis[a]
PCI (6 months)	n=65[a] 9%	n=40 22%	p=0.072 Per protocol analysis[a]
CABG (6 months)	n=65[a] 1.6%	n=40 0%	p=NS Per protocol analysis[a]
All-cause mortality (3 years)	n=79 4/79 (3.4%)	n=40 0/40 (0%)	n=119/121=98.3% p=0.30
Re-PCI	15/79 (19%)	13/40 (32.5%)	p=0.10
Re-PCI NCL	7/79 (8.9%)	13/40 (32.5%)	p=0.001
Re-PCI CL	8/79 (10.1%)	0/40 (0%)	p=0.05
CABG	12/79 (15.2%)	1/40 (2.5%)	p=0.05
Re-MI	14/79 (17.7%)	0/40 (0%)	p=0.002
MACE	28/79 (35.4%)	14/40 (35%)	p=0.96
Death and/or MI	16/79 (20.3%)	0/40 (0%)	p=0.002
Safety	n=80	n=41	

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Coronary dissection	n=1	-	Coronary dissection caused by FFR wire
Acute vessel closure	n=1	-	Acute vessel closure after FFR but before PCI leading to CABG and death within several days
non-STEMI	n=2	-	non-STEMI after FFR-guided PCI due to side branch occlusion
Major bleeding	n=5	n=1	Defined by needing transfusion or surgery
Subacute stent thrombosis	n=3	-	Subacute stent thrombosis within 30 days
CI, confidence interval; EF, ejection fraction; ITT, intention to treat; n, number of patients; NS, non-standardised; PCI-ICL, percutaneous coronary intervention, culprit lesion; PCI-NCL, percutaneous coronary intervention, non-culprit lesion; RR, relative risk; STEMI, ST-segment elevated myocardial infarction. [a] The 65 patients are those who underwent at least one FFR measurement.			

Register data

Li et al. (2013)

This retrospective cohort study included 7358 consecutive patients referred for PCI at the Mayo Clinic, Rochester, USA between October 2002 and December 2009. It aimed to study the long-term outcomes of FFR-guided PCI compared with PCI procedures performed without FFR. FFR measurement used both PressureWire FFR devices and competitor products. Generally, FFR-guided treatment proceeded to PCI if the FFR was less than 0.75, and PCI was deferred if the FFR was greater than 0.8. For FFR values between 0.75 and 0.8, treatment was left to the operator's judgement.

The study is summarised in tables 10 and 11.

Unadjusted analyses showed improved outcomes at 7 years for all combinations of MACE-related outcomes for FFR-guided PCI compared with PCI without prior FFR measurement. When analyses

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were adjusted for multiple risk factors there were no differences between the groups at 7 years for any MACE-related outcome.

Unadjusted analyses of patients in the FFR-guided strategy found that patients who proceeded to PCI had a significantly higher rate of MI at 7 years than those who did not (p=0.007). Adjusting for multiple risk factors did not change these findings.

The authors concluded that the study supports the use of FFR for decision-making in patients undergoing cardiac catheterisation.

Table 10 Summary of the cohort study reported by Li et al. [2013]

Study component	Description
Objectives / hypotheses	To study the long term outcomes of FFR guided PCI in general clinical practice, comparing outcomes after FFR-guided PCI with outcomes after angiography-guided PCI
Study design	Retrospective cohort study of 7358 patients at 1 site
Setting	Consecutive patients referred for PCI at the Mayo Clinic, Rochester, USA between October 2002 and December 2009
Inclusion / exclusion criteria	A register of all patients referred for coronary revascularisation at the Mayo Clinic started in October 2002. Exclusion criteria included presentation with ST-segment elevation MI (STEMI) or cardiogenic shock, referral for coronary artery bypass surgery, or lack of consent From 8942 procedures performed, 220 were excluded due to denial of research authorisation, 1360 met exclusion criteria, and 7358 were eligible for analysis Patients were followed up by telephone at 3 months, 6 months, 12 months and then annually. Information was retrieved from medical records. For patients with deferred PCI, follow-up was by a single questionnaire and history review Follow-up information was available in 7050 (95.8%) of patients. The median follow-up duration was 44.9 months for PCI only, 52.5 months for FFR PERFORM, and 48.7 months for FFR DEFER.
Variables	There was no clearly stated primary outcome. Reported outcomes included MACE, death, MI and emergency revascularisation

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Statistical methods	Students' 2-sample t-test for most continuous variables Rank sum test for FFR comparisons Pearson's x2 test for discrete data Kaplan-Meier estimates to estimate survival curves, and the log-rank test to test differences between groups Cox proportional hazards multiple regression models to estimate association between FFR use versus deferral on long-term outcomes All significance tests were 2-tailed with a 0.05 significance level Analyses were conducted using SAS 9.2
Participants	Of the included 7358 patients, 6268 (85.2%) underwent PCI without FFR assessment. In the remaining 1090 (14.8%) patients, FFR was performed. From these 369 (33.9% of FFR) patients received PCI, and in 721 (66.1% of FFR) PCI was deferred. In 115 (10.5% of FFR) patients PCI was performed where FFR>0.8, and in 39 (3.6%) of patients no PCI was performed where FFR<0.75
Main results	1. Unadjusted analyses: FFR (and PCI only if indicated by FFR) strategy versus straight to PCI strategy: the FFR group had better outcomes at 7 years for all combinations of cardiac event outcomes. This could be due to better selection of patients for PCI due to FFR, or it could reflect those in the FFR group being fitter at baseline2. Unadjusted analyses: of patients who received FFR, those who underwent PCI in response to FFR had poorer outcome at 7 years than those who had no PCI – in terms of MI only. There was no difference for other cardiac events 3. Adjusted analyses: FFR (and PCI only if indicated by FFR) strategy versus straight to PCI strategy: there were no longer differences between groups at 7 years for any MACE-related outcome 4. Adjusted analyses: of patients who received FFR, those who underwent PCI in response to FFR had a poorer outcome at 7 years in terms of MI than those in whom PCI was deferred. There was no difference in other MACE related outcomes
Conclusions	Authors' conclusions: In current practice, FFR-guided treatment is associated with a favourable long-term outcome. The study supports the use of the FFR for decision-making in patients undergoing cardiac catheterisation.

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CI, confidence interval; ITT, intention to treat; n, number of patients; RR, relative risk; SAS, supra-regional assay service.

The study was retrospective, so treatment decisions, including those based on FFR diagnostic information, were made without a trial protocol. FFR may have been selectively used in 'fitter' patients for whom a decision about whether to do PCI was more difficult. Baseline risk factor data appear to support this.

Table 11: Results of the cohort study reported by Li et al. (2013)

	PCI only	All FFR	FFR Perform	FFR Defer	Analysis
Randomised	n=6268	n=1090	n=369	n=721	
Efficacy	n=6268 193 (3.1%) lost		n=369 17 (4.6%) lost	n=721 108 (15.0) lost	ITT
Primary outcome: MACE	57%	50%			p=0.016 7 year follow-up. Unadjusted Kaplan-Meier analysis
Selected secondary outcomes: Mortality	32%	21%			p<0.001 7 year follow-up. Unadjusted Kaplan-Meier analysis
MI	15%	8%			p<0.001 7 year follow-up. Unadjusted Kaplan-Meier analysis
Mortality or MI	41%	26%	-	-	p<0.001 7 year follow-up. Unadjusted Kaplan-Meier analysis

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Repeat revascularisation	36%	35%	-	-	p=0.97 7 year follow-up. Unadjusted Kaplan-Meier analysis
MI	-	-	12%	6%	7 year follow-up. Unadjusted Kaplan-Meier analysis
7 year follow-up. Adjusted[b] Cox multivariable model					
			Analysis		
MACE			HR (All FFR:PCI) 1.01 (95% CI 0.89–1.14), p=0.93		
Death			HR (All FFR:PCI) 0.89 (95% CI 0.73–1.10), p=0.28		
MI			HR (All FFR:PCI) 0.79 (95% CI 0.26–0.82), p=0.12		
Death / revascularisation			HR (All FFR:PCI) 1.003 (95% CI 0.88–1.14), p=0.96		
Death / MI			HR (All FFR:PCI) 0.85 (95% CI 0.711.01), p=0.06		
MACE			HR (FFR-DEFER:FFR-PERFORM) 0.97 (95% CI 0.77-1.23), p=0.81		
Death			HR (FFR-DEFER:FFR-PERFORM) 0.84 (95% CI 0.56–1.24), p=0.37		
MI			HR (FFR-DEFER:FFR-PERFORM) 0.46 (95% CI 0.26–0.82), p=0.008		
Death / revascularisation			HR (FFR-DEFER:FFR-PERFORM) 1.002 (95% CI 0.78–1.27), p=0.98		
Death / MI			HR (FFR-DEFER:FFR-PERFORM) 0.73 (95% CI 0.52–1.01), p=0.06		
Safety	n=6268		n=369	n=721	

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CI, confidence interval; FFR, fractional flow reserve; ITT, intention to treat; n, number of patients; RR, relative risk.

[a] This was the only outcome between FFR-PERFORM and FFR-DEFER that reported significance.

[b] Adjusted for age, sex, body mass index, smoking history, chronic heart failure on presentation, diabetes, hypertension, hypercholesterolaemia, primary symptom, recent MI, prior PCI, prior CABG, history of MI, heart failure, cerebral vascular disease, peripheral artery disease, chronic obstructive pulmonary disease, renal dysfunction, presence of tumour/lymphoma/leukaemia, metastatic cancer, ejection fraction ≤40%, ejection fraction unknown, level of stenosis in each coronary vessel (right coronary artery, left anterior descending, left circumflex, left main coronary artery).

Most of the results are presented in the paper graphically, and without the information needed to present them numerically.

Ongoing clinical trials

Ten ongoing or in-development studies using FFR as a decision tool for treatment of coronary artery disease were identified, including the UK-based RIPCORD trial, in the preparation of this briefing (NCT01764334; NCT01835808; NCT01175863; NCT01132495; NCT01399736; NCT01366404; NCT01881555; NCT01810224; NCT01070771; NCT01960933).

Costs and resource consequences

In a 2012 audit carried out by the British Cardiovascular Interventional Society, it was reported that FFR was used in 113 centres in the UK out of a total of 178 (118 that carry out PCI, 60 that do diagnostic angiography only). Of 241,240 diagnostic angiography procedures, 7630 included FFR measurement (3.1%). There were also 92,445 PCI procedures, of which 6132 included FFR (6.6%), although there was significant variation in these proportions between centres (Ludman 2013a). In a UK regional cardiology centre, 6.2% of patients (100/1621) with NSTEMI had FFR measured over a 15 month period in 2009–10 (Carrick et al. 2011; Carrick et al. 2013). It is not known what proportion of these procedures used either of the 2 PressureWire FFR devices.

Many centres already use devices that measure FFR, but for others (for example, diagnostic-only centres) additional training and new protocols would be needed. Competency-based training for interventional cardiologists and support staff is provided by the manufacturer. This is included in the cost of the device and depends on the needs of the centre.

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The PressureWire Aeris is claimed to be compatible with 'all major hemodynamic recording systems' so it should be suitable for most cardiac catheterisation laboratories with systems that have FFR capability. Proprietary monitoring systems are needed for the PressureWire Certus (with Agile tip).

Measuring FFR takes an additional 5–20 minutes during angiography or PCI.

FFR measurements during PCI are reimbursed in the NHS in England via the Payment by Results tariff and are covered by Health Resource Group (HRG) code EA49Z. In the 2013–14 tariff, this is £3262 for elective procedures and £4440 for non-elective procedures. In the 2014–15 tariff, FFR when used with arteriography only will be covered by HRG code EA35Z. The tariff values for EA35 in 2014–15 will be £2092 for elective procedures and £3393 for non-elective procedures.

Four published economic analyses have been identified, all of which used PressureWire FFR devices.

Fearon et al. (2003)

Fearon et al. (2003) created a decision tree model for patients with chest pain in whom intermediate lesions were detected during angiography. The authors reported that FFR-guided stenting during angiography was US $3830 cheaper than stenting all patients and US $1795 cheaper than deferring PCI until a nuclear perfusion stress test is conducted. All 3 strategies had a similar quality-adjusted survival, although the quality-adjusted life year (QALY) for the stenting strategy was slightly lower than that for the FFR strategy. Although the authors state that in the US, PCI is often delayed for non-invasive testing after intermediate lesions are detected, it is not known whether this represents current practice in the UK. It is also unlikely that a strategy of stenting all intermediate lesions would be ethical because of the additional risk of implanting a stent.

Fearon et al. (2010), FAME

Fearon et al. (2010) conducted an economic analysis using resource data and outcomes from the FAME international multicentre randomised controlled trial. This study used international data but was conducted in the context of the US healthcare system. A population of 1005 patients with multi-vessel coronary artery disease who were indicated for PCI were randomised to either angiography-guided PCI or FFR-guided PCI. Patient utility was determined using survival and quality of life measures at 1 month and 1 year. FFR-guided PCI was reported to be less costly than angiography-guided PCI for both the index procedure (US $13,182 ±US $9667 versus US$ 14,878 ±US $9509) and the total 1 year costs (US$14315 ±US $11,109 compared with US

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$16,700 ±US $11,868). Despite the wide variation in values these differences were highly statistically significant (p<0.0001) and robust to bootstrap simulations (cost saving in 91% of simulations). Ninety per cent of the costs were incurred during the index procedure and were primarily dependent on the costs of drug-eluting stents, cardiac unit bed days and the FFR devices (US $650 each).

Baseline utility was slightly higher in the FFR-guided group (significance not reported) and this difference was corrected for by offsetting (half the difference was added to the angiography-guided group and half was subtracted from the FFR-guided group). Offset utility increased at 1 month and remained stable at 1 year for both groups and was not statistically significantly different between the groups (p=0.2 at 1 year). These results should be interpreted with caution given that the patient population was pre-determined to receive PCI for 2 or 3 lesions. The use of FFR-guided PCI was highly likely to reduce the number of stents used and the cost of the PressureWire FFR devices is US $1450 less than the cost of the drug-eluting stent (Hoole et al. 2011).

The PressureWire device was cost effective for the group of patients in whom 2 or more lesions were already determined by angiography to be treated with PCI. The cost saved by reducing the number of stents in some patients was greater than the cost incurred by using PressureWire FFR devices on all of the patients.

Hoole et al. (2011)

Hoole et al. (2011) conducted a retrospective analysis of 100 intermediate lesions, of which 50 had an FFR of greater than 0.80, in a Canadian general hospital. Three independent interventional cardiologists blinded to the FFR value and actual treatment provided a theoretical treatment plan. 7 fewer stents were used with an angiography-guided decision compared with FFR values. The authors indicated that this reduction in the number of stents plus the additional cost of the PressureWire FFR device would result in the FFR-guided strategy being cost-incurring with respect to angiography guidance. However, this is a simplistic analysis only comparing the technology costs during the index procedure and ignoring any health and resource outcomes from not using stents.

Fearon et al. (2013), FAME II

Fearon et al. (2013) conducted an economic analysis from a US perspective using resource data and outcomes from the FAME II trial. A population of 888 patients with stable angina and coronary artery disease for whom PCI was appropriate and who had an FFR of less than 0.80 were randomised to either FFR-guided PCI plus medical therapy or medical therapy only. Patient utility

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was determined using quality of life measures at 1 month and projected assuming a linear decline to baseline over 3 years (as the trial was stopped early). FFR-guided PCI incurred costs with respect to medical therapy for the initial hospitalisation (US $9927 compared with US $3900, p<0.001), primarily as a result of the PCI procedure. The cost difference reduced over the following year, primarily as a result of a higher rate of revascularisations in the medical therapy arm, but were still significantly higher in the FFR strategy arm (US $12,646 compared with US $9763, p<0.001).

Change in patient utility from baseline to 1 month was significantly higher in the FFR arm compared with medical treatment (0.054 compared with 0.001 respectively, p<0.0001). If these utility differences declined linearly over 3 years and costs beyond 1 year did not change, the incremental cost-effectiveness ratio (ICER) of FFR compared with medical therapy was determined to be US $36,000/QALY. This value was below a maximum acceptable ICER of US $50,000/QALY in 80% of bootstrap simulations.

These results should be interpreted with caution as the patient population was defined as patients with 'significant myocardial ischaemia caused by a coronary lesion amenable to PCI'. NICE clinical guideline 126 states that, for patients whose angina symptoms are not controlled by medical treatment, angiography and additional functional testing should be considered. It is not clear if the patients in this study had poorly controlled symptoms, although they did have angiographically demonstrated stenosis and PCI was considered appropriate for them. A possible interpretation is that some patients randomised to medical treatment were undertreated, as they would have received PCI if not in the trial.

Economic analyses relevant to NHS use

Bornstein et al. (2011), Siebert et al. (2011a) and Siebert et al. (2011b) conducted economic analyses using data from the FAME study in the context of the healthcare systems of several European countries, including the UK. These studies were only reported as conference abstracts and so provide only a small amount of information. Cost savings in Germany, UK and Italy are reported as ranging from 300–600 Euros per patient if an FFR-guided strategy was used in comparison to angiography-guided PCI in patients already indicated for PCI. As in Fearon et al. (2010) these figures do not necessarily represent the use of FFR-guided decision-making in patients with angina whose stenosis status is unknown and in whom suitability for PCI is undetermined.

No published economic analyses based in the UK were identified.

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Strengths and limitations of the evidence

The evidence comes from 3 large multicentre randomised controlled trials, 1 single centre randomised controlled trial and 1 large registry. This is a strong evidence level compared with many other medical technologies.

In all of the randomised controlled trials neither clinicians nor patients were blinded to treatment, although in some an adjudication panel that considered adverse events was blinded to treatment. Blinding is frequently very difficult to achieve in trials of medical devices. The single-centre trial did not recruit the full number of patients and was underpowered, meaning that a finding of no significant difference was inconclusive.

In some instances, differences between the treatment arms did not reach statistical significance (at $p<0.05$) when data were analysed using the planned method. When outcomes are re-defined, differences may appear to reach statistical significance. There is an increased likelihood of detecting a difference between the arms purely by chance (type I error) associated with carrying out multiple statistical tests on the same data, but the authors did not correct for this. As such, results for redefined outcomes that appear to reach statistical significance (at $p<0.05$) should be interpreted with caution.

A key consideration for all the trials is to understand the context of current care pathways in the NHS and the setting for the trial. The interpretation of the results depends on the assumptions about the treatment the patients would have received had they not been participating in a trial, and if the same patients would have received that treatment within the NHS.

There were many more men recruited to the trials than women, reflecting disease prevalence. However, Kim et al. (2012) addressed this in a reanalysis of the FAME data.

The register data included information from procedures carried out with both PressureWire FFR devices and other guidewire devices with FFR capability.

Relevance to NICE guidance programmes

The use of the PressureWire fractional flow reserve devices is not currently planned into any NICE guidance programme.

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References

Bech GJW, De Bruyne B, Bonnier HJR M et al. (1998) Long-Term Follow-Up After Deferral of Percutaneous Transluminal Coronary Angioplasty of Intermediate Stenosis on the Basis of Coronary Pressure Measurement. Journal of the American College of Cardiology 31: 841–847

Bech, GJ, De Bruyne B, Pijls NH et al. (2001a) Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation 103: 2928–2934

Bech GJW, Droste H, Pijls NH et al. (2001b) Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. Heart 86: 547–552

Blue Cross and Blue Shield Association Technology Evaluation Center (2011) Fractional flow reserve and coronary artery revascularization, Report 26

Boden W. (2012) Which Is More Enduring — FAME or COURAGE? The New England Journal of Medicine 367: 1059–1061

Bornschein B, Arvandi M, Gothe R et al. (2011) Cost effectiveness of fractional flow reserve measurement in multivessel coronary artery disease in Belgium and France. Value in Health 14: A233–A510

Botman KJ, Pijls NH, Bech JW et al. (2004) Percutaneous coronary intervention or bypass surgery in multivessel disease? A tailored approach based on coronary pressure measurement. Catheterization and Cardiovascular Interventions 63: 184–191

Carrick D, Behan M, Foo F et al. (2011) Influence of fractional flow reserve measurement on treatment-decisions in patients with recent acute non-ST elevation myocardial infarction. Heart 97: A16–A17

Carrick D, Behan M, Foo F et al. (2013) Usefulness of Fractional Flow Reserve to Improve Diagnostic Efficiency in Patients With Non-ST Elevation Myocardial Infarction. The American Journal of Cardiology 111: 45–50

Chamuleau SAJ, Meuwissen M, Koch KT et al. (2002) Usefulness of fractional flow reserve for risk stratification of patients with multivessel coronary artery disease and an intermediate stenosis. The American Journal of Cardiology 89: 377–380

© NICE 2018. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Dambrink JH, Debrauwere JP, Van 't Hof AWJ et al. (2010) Non-culprit lesions detected during primary PCI: Treat invasively or follow the guidelines? EuroIntervention 5: 968-975

Dawkins KD, Gershlick T, de Belder M et al. (2005) Percutaneous coronary intervention: recommendations for good practice and training. Heart 91: vi1–vi27

De Bruyne B, Pijls NH, Kalesan B et al. (2012) Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. New England Journal of Medicine 367: 991–1001

Fearon WF, Bornschein B, Tonino PA et al. (2010) Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. Circulation 122: 2545–2550

Fearon WF, Shilane D, Pijls NH et al. (2013) Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. Circulation 128: 17: 1335-1340

Fearon WF, Tonino PA, De Bruyne B et al. (2007) Rationale and design of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study. American Heart Journal 154: 632–636

Fearon WF, Yeung AC, Lee DP et al. (2003) Cost-effectiveness of measuring fractional flow reserve to guide coronary interventions. American Heart Journal 145: 882–887

Ghani A, Dambrink JH, Van't Hof AWJ et al. (2012) Treatment of non-culprit lesions detected during primary PCI: Long-term follow-up of a randomised clinical trial. Netherlands Heart Journal 20: 347–353

Health & Social Care Information Centre. HRG4 2014/15. Consultation Grouper HRG4 Chapter Summaries. [Accessed 16th January 2014]

Hernandez-Garcia JM, Alonso-Briales JH, Jimenez-Navarro M et al. (2001) Clinical Management of Patients with Coronary Syndromes and Negative Fractional Flow Reserve Findings. Journal of Interventional Cardiology 14: 505–510

Hoole SP, Seddon MD, Poulter RS et al. (2011) Fame comes at a cost: a Canadian analysis of procedural costs in use of pressure wire to guide multivessel percutaneous coronary intervention. Canadian Journal of Cardiology 27: 2: 262.e1–262.e2

© NICE 2018. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Jasti V, Ivan E, Yalamanchili V, et al. (2004) Correlations Between Fractional Flow Reserve and Intravascular Ultrasound in Patients With an Ambiguous Left Main Coronary Artery Stenosis. Circulation 110: 2831–2836

Jimenez-Navarro M, Hernandez-Garcia JM, Alonso-Briales JH et al. (2004) Should we treat patients with moderately severe stenosis of the left main coronary artery and negative FFR results? Journal of Invasive Cardiology 16: 398–400

Kim HS, Tonino PA, De Bruyne Bet al. (2012) The impact of sex differences on fractional flow reserve-guided percutaneous coronary intervention: a FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) substudy. JACC.Cardiovascular Interventions 5: 1037–1042

Leesar MA, Abdul-Baki T, Akkus NI et al. (2003) Use of fractional flow reserve versus stress perfusion scintigraphy after unstable angina. Effect on duration of hospitalization, cost, procedural characteristics, and clinical outcome. Journal of the American College of Cardiology 41: 1115–1121

Legalery P, Schiele F, Seronde MF et al. (2005) One-year outcome of patients submitted to routine fractional flow reserve assessment to determine the need for angioplasty. European Heart Journal 26: 2623–2629

Li J, Elrashidi MY, Flammer AJ et al. (2013) Long-term outcomes of fractional flow reserve-guided vs. angiography-guided percutaneous coronary intervention in contemporary practice. European Heart Journal 34: 1375–1383

Lindstaedt M, Yazar A, Germing A et al. (2006) Clinical outcome in patients with intermediate or equivocal left main coronary artery disease after deferral of surgical revascularization on the basis of fractional flow reserve measurements. American Heart Journal 152: 15

Lopez-Palop R, Pinar E, Lozano I et al. (2004) Utility of the fractional flow reserve in the evaluation of angiographically moderate in-stent restenosis. European Heart Journal 25: 2040–2047

Ludman, P (2013a) BCIS Audit Returns 2012: adult interventional procedures

Ludman, P (2013b) National Audit of Percutaneous Coronary Interventional Procedures: annual public report (January 2011–December 2011), National Institute for Cardiovascular Outcomes Research (NICOR)

© NICE 2018. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Medical Services Advisory Committee (MSAC) (2005) Coronary pressure wire: MSAC application 1080.

Meuwissen M, de Winter RJ, Chamuleau SAJ et al. (2003) Value of C-reactive protein in patients with stable angina pectoris, coronary narrowing (30% to 70%), and normal fractional flow reserve. The American Journal of Cardiology 92: 702–705

Montalescot G, Sechtem U, Achenbach Set al. (2013) ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. European Heart Journal 34: 2949–3003

Muramatsu T, Tsukahara R, Ho M et al. (2002) Usefulness of fractional flow reserve guidance for PCI in acute myocardial infarction. The Journal of Invasive Cardiology 14: 657–662

Nam CW, Mangiacapra F, Entjes et al. (2011) Functional SYNTAX score for risk assessment in multivessel coronary artery disease. Journal of the American College of Cardiology 58: 1211–1218

National Institute for Health and Clinical Excellence (2012) Management of stable angina NICE clinical guideline 126

National Institute for Health and Clinical Excellence (2010) Unstable angina and NSTEMI. NICE clinical guideline 94

Ozdemir M, Timurkaynak T, Cemri M et al. (2002). Medium-term follow-up of intermediate coronary stenoses left unrevascularized based on myocardial fractional flow reserve findings. Acta Cardiologica 57: 335–340

Patel MR (2013) Fractional Flow Reserve and the Appropriate Use Criteria: determining best practices in coronary revascularization. Cardiac Interventions Today Jan–Feb 2013: 64–74

Patel MR, Bailey SR, Bonow RO et al. (2012). Appropriate Use Criteria for Diagnostic Catheterization: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force. Journal of the American College of Cardiology 59: 1995–2027

Pijls NH, De Bruyne B, Peels K et al. (1996) Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. New England Journal of Medicine 334: 1703–1708

© NICE 2018. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights).

Pijls NH, Fearon WF, Tonino PA et al. (2010) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. Journal of the American College of Cardiology 56: 177–184

Pijls NH, van Schaardenburgh P, Manoharan G et al. (2007) Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. Journal of the American College of Cardiology 49: 2105–2111

Raman G, Yu W, Ip S et al. (2013) Intravascular diagnostic procedures and imaging techniques versus angiography alone in coronary artery stenting: comparative effectiveness review. 104

Reczuch K, Jankowska E, Telichowski A et al. (2004) Measurement of fractional flow reserve in patients with multi-vessel coronary artery disease and borderline lesions prevents unnecessary revascularisation procedures. Kardiologia Polska 60: 311–319

Rieber J, Schiele TM, Koenig A et al. (2002) Long-term safety of therapy stratification in patients with intermediate coronary lesions based on intracoronary pressure measurements. The American Journal of Cardiology 90: 1160–1164

Sels JW, Tonino PA, Siebert U et al. (2011) Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. JACC: Cardiovascular Interventions 4:1183–1189

Siebert U, Bornschein B, Arvandi MS et al. (2011a). Cost-effectiveness and public health/budget-impact of ffr-guided PCI in multivessel patients in 6 European countries – analysis along the FAME trial data. Society for Medical Decision Making (SMDM) 33rd Annual Meeting

Siebert U, Bornschein B, Arvandi MS et al. (2011b) Cost-effectiveness and public health and budget-impact of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease in Germany. Health Technology Assessment Society (HTAi) 8th Annual Meeting

Siebert U, Bornschein B, Schnell-Inderst P et al. (2008) Measurement of fractional flow reserve to guide decisions for percutaneous coronary intervention. GMS Health Technology Assessment 4: 7

Tonino PA, De Bruyne B, Pijls NH et al. (2009) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. New England Journal of Medicine 360: 213–224

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Tonino PA, Fearon WF, De Bruyne Bet al. (2010) Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. Journal of the American College of Cardiology 55: 2816–2821

Wijns W, Kolh P, Danchin Net al. (2010) Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal 31: 2501–2555

Wongpraparut N, Yalamanchili V, Pasnoori Vet al. (2005) Thirty-month outcome after fractional flow reserve-guided versus conventional multivessel percutaneous coronary intervention. American Journal of Cardiology 96: 877–884

Search strategy and evidence selection

Search strategy

Medline (1946 to present) was searched with the following strategy on 24th October 2013.

1. exp Coronary Restenosis/

2. exp Coronary Stenosis/

3. exp Coronary Disease/

4. exp Coronary Artery Disease/

5. exp Myocardial Ischemia/

6. exp Acute Coronary Syndrome/

7. exp Angina Pectoris/

8. exp Myocardial Infarction/

9. exp Angioplasty, Balloon/

10. exp Angioplasty, Laser/

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11. exp Angina, Stable/

12. exp Angina, Unstable/

13. exp Coronary Angiography/

14. exp Myocardial Revascularization/

15. exp Coronary Artery Bypass/

16. exp Percutaneous Coronary Intervention/

17. exp Angioplasty/

18. exp Stents/

19. exp Drug-Eluting Stents/

20. (coronary adj3 intervention*).tw.

21. exp Fractional Flow Reserve, Myocardial/

22. fractional flow reserve.tw.

23. FFR.tw.

24. (pressure adj3 (wire or guidewire or catheter* or sensor)).tw.

25. (radi adj2 press*).tw.

26. (radi adj2 wire*).tw.

27. exp Random Allocation/

28. exp Randomized Controlled Trials as Topic/

29. exp Randomized Controlled Trial/

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30. (randomi#ed adj5 trial).ti,ab.

31. (randomi#ed adj5 study).ti,ab.

32. randomly allocated.tw.

33. (allocated adj2 random*).tw.

34. exp Meta-Analysis/

35. exp Meta-Analysis as Topic/

36. meta analy*.tw.

37. metaanaly*.tw.

38. (systematic* adj (review*1 or overview*1)).ti,ab.

39. (Cochrane adj2 review).mp.

40. or/1-20

41. or/21-26

42. or/27-39

43. and/40-42

44. 43

45. limit 44 to english language

46. limit 45 to humans

47. limit 46 to year='2003 -Current"

The initial search was not restricted to randomised controlled trials and systematic reviews and returned over 1000 hits in Medline and over 1700 hits in Embase. It became apparent that papers

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could not be quickly sorted by title and abstract, as there are many papers that compare the diagnostic accuracy of fractional flow reserve (FFR) with other techniques, use FFR as an outcome, or as a comparator, in addition to reviews and editorials. There were also several randomised controlled trials with large patient numbers. Therefore the formal search was restricted to randomised controlled trials and systematic reviews when searching large databases. The search was also restricted to after 2003, due to the availability of a good quality systematic review published in 2005 (Medical Services Advisory Committee (MSAC) 2005).

Databases searched were MEDLINE, Embase, Cochrane Library, DARE (including CRD, NHS EED & HTA) and PubMed. A search was completed for ongoing clinical trials.

Evidence selection

The initial search resulted in 151 entries. It was performed by 2 independent reviewers based on title and abstract, and the following criteria:

- Population: general cardiac interventions.
- Intervention: FFR using PressureWire FFR devices to decide if PCI needed.
- Comparator: standard care – angiography.
- Outcomes: include all reported.

The initial search resulted in 42 papers (including 1 duplicate). These were obtained as full text. A second selection was made by one reviewer, and checked by a second reviewer.

The final selection included clinical information from 2 systematic reviews and information on 4 randomised controlled trials (in 8 papers). A further 4 papers were selected for economic information. In addition 1 systematic review and 1 retrospective registry analysis were identified informally and were included.

Table 12: Papers included in systematic reviews

Study	Paper	Raman 2013	TEC 2011	MSAC 2005
FAME	Fearon et al. (2010)	?		
FAME	Pijls et al. (2010)	?	?	
FAME	Tonino et al. (2009)	?	?	

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	Wongpraparut et al. (2005)	?	?	
	Muramatsu et al. (2002)	?		
FAME	Nam et al. (2010)	?		
FAME II	De Bruyne et al. (2012)	Excluded		
DEFER	Pijls et al. (2007)	Excluded	?	
DEFER	Bech et al. (2001a)	-	?	?
-	Chamuleau et al. (2002)		?	
-	Legalery et al. (2005)		?	
-	Lindstaedt et al. (2006		?	
-	Leesar et al.(2003)			?
-	Bech et al. (2001b)			?
-	Botman et al. (2004)			?
-	Jasti et al. (2004)			?
-	Jimenez-Navarro et al. (2004)			?
-	Lopez-Palop et al. (2004)			?
-	Reczuch et al. (2004)			?
-	Rieber et al. (2002)			?
-	Bech et al. (1998)			?
-	Hernandez-Garcia et al. (2001)			?
-	Meuwissen et al. (2003)			?
-	Ozdemir et al. (2002)			?
-	Pijls et al. (1996)			?

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers, and procurement professionals.

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Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance.**

Development of this briefing

This briefing was developed for NICE by Cedar. The Interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality assured and approved for publication.

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