Comparative Effectiveness Review
Number 104

Effective Health Care Program

Intravascular Diagnostic Procedures and Imaging Techniques Versus Angiography Alone in Coronary Artery Stenting: Comparative Effectiveness Review

Executive Summary

Background

Coronary artery disease (CAD) involves narrowing (stenosis) of one or more of the epicardial coronary arteries. CAD is most commonly a result of buildup of plaque (atherosclerosis), which impedes the ability of the blood vessels to deliver oxygenated blood to the heart muscle (myocardium). Revascularization is a commonly accepted treatment for patients with CAD, and options vary according to the presentation of CAD, either as acute (myocardial infarction [MI]) or chronic (refractory chest pain, also known as angina). Percutaneous coronary intervention (PCI) with stent deployment is currently the most commonly performed revascularization procedure for CAD.

In determining the proper treatment course for patients with CAD, a number of treatment decisions must be made, including whether a particular lesion can be treated with medical therapy alone or whether the lesion requires PCI or bypass grafting. If PCI is prescribed, the particulars of how to stent the lesion (stent size, length, material, and positioning) must be determined; and, following the procedure, it must be determined whether or not stenting was successful.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

PCI with stent deployment has traditionally been based on coronary angiography, an imaging technique for visualizing the interior of blood vessels that can be

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analyzed either qualitatively (with visual inspection of the radiocontrast lumenogram) or quantitatively (with computer-based quantitation). While angiography is the standard technique for the anatomic imaging of coronary arteries, it only visualizes an outline of the interior of the luminal wall. Angiography has a limited ability to determine the functional severity of intermediate ranges of coronary stenoses (40% to 70%). Angiography often underestimates or overestimates lumen dimensions; therefore, using angiography alone in the diagnosis of lesions could lead to an underestimate of stenosis severity, possibly deferring a clinically indicated revascularization procedure, or to an overestimate of stenosis severity, possibly leading to unnecessary stenting procedures. Furthermore, angiographic quantification is insufficient to map the detailed morphology of complex lesions—particularly those in the left main coronary artery—and in providing information on the composition of coronary plaques. In addition, it is difficult to assess by angiography alone whether a stent has fully expanded and apposed to the intraluminal border after stent implantation.

In order to address these limitations, several adjunctive intravascular diagnostic procedures and imaging techniques (collectively referred to as intravascular diagnostic techniques in this report) have been developed to assist in treatment decisionmaking, by providing more detailed anatomic and hemodynamic information on coronary stenoses. Intravascular diagnostic techniques do not preclude the use of angiography but rather are complementary procedures.[1] For example, one such intravascular diagnostic technique, fractional flow reserve (FFR)—the ratio of maximal blood flow in a stenotic coronary artery to normal maximal flow—is used during coronary angiography to determine the physiological (functional) severity of coronary stenoses as opposed to simply visualizing anatomy with angiography. In this way, FFR may aid in deciding whether a lesion needs to be stented or whether stenting can be deferred.[2,3] Other less commonly used techniques to determine the physiological severity of coronary stenosis include coronary flow reserve and tests that measure stenosis index and index of microcirculatory resistance.

Intravascular imaging techniques are used to guide treatment decisionmaking by enhancing visualization of coronary lesions. Among such imaging techniques, intravascular ultrasound (IVUS) is the most commonly used. IVUS augments angiography by providing precise lesion characteristics, such as minimal and maximal lumen diameters, cross-sectional area, and plaque area. Other imaging techniques for visualizing coronary anatomy that are less commonly used or are still evolving include IVUS-virtual histology, integrated backscatter IVUS, optical coherence tomography (OCT), near-infrared spectroscopy (NIRS), angioscopy, thermography, and intravascular magnetic resonance imaging (IMRI). These techniques are described in detail in the full report.

While intravascular diagnostic techniques do provide additional anatomic or hemodynamic information during PCI, they are invasive techniques, and their application can result in procedure-related complications, increased procedural times, and high initial costs. The use of these adjunctive invasive procedures can also lead to additional invasive tests or treatments that can adversely impact long-term clinical outcomes. Therefore, it is important to assess whether the additional diagnostic information produced actually translates into benefits for patients that outweigh the risks.

Current systematic reviews have not comprehensively examined the role of intravascular diagnostic technique utilization in relation to tertiary care and other hospital settings, and are not generally applicable to contemporary practice, as recent literature has not yet been thoroughly reviewed (e.g., application of intravascular diagnostic techniques during PCI and deployment of newer drug-eluting stents). Furthermore, variation in how intravascular diagnostic techniques are adopted in clinical practice across catheterization laboratories reflects the uncertainty regarding the utility and role of the techniques.

Objectives

This Comparative Effectiveness Review (CER) systematically evaluates the effectiveness of intravascular diagnostic techniques versus angiography alone, as well as among other intravascular diagnostic techniques, in patients with CAD who are undergoing coronary artery stenting. This review also evaluates the factors influencing the effect of intravascular diagnostic techniques on outcomes, as compared with angiography alone (or other intravascular diagnostic techniques).

Methods

Input From Stakeholders

This project began with a topic refinement in which Key Questions were proposed and refined by a panel of Key Informants. The panel included experts in interventional cardiology, interventional radiology, and noninterventional cardiology; representatives from relevant specialty societies; payers; and a patient representative.

Subsequently, during the CER phase, we reconvened a Technical Expert Panel who provided clinical expertise in translating the Key Questions into a research protocol by specifying the patient populations, interventions, comparators, outcomes, and study designs of interest.

Key Questions

Our review focused on five Key Questions:

Key Question 1: In patients with CAD, what is the impact of using an intravascular diagnostic technique and angiography in deciding whether a coronary lesion requires intervention—when compared with angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Question 2: For patients undergoing PCI, what is the impact of using an intravascular diagnostic technique and angiography to guide the stent placement (either immediately prior to or during the procedure)—when compared with angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Question 3: For patients having just undergone a PCI, what is the impact of using an intravascular diagnostic technique and angiography to evaluate the success of stent placement immediately after the procedure—when compared with angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Key Question 4: How do different intravascular diagnostic techniques compare to each other in their effects on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

a. During evaluation of the presence/extent of CAD and the potential necessity of coronary intervention?

b. During PCI to guide stent placement?

c. Immediately after PCI to evaluate the success of stent placement?

Key Question 5: What factors (e.g., patient/physician characteristics, availability of prior noninvasive testing, type of PCI performed) influence the effect of intravascular diagnostic techniques and angiography—when compared with angiography alone (or among different intravascular diagnostic techniques)—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

a. During evaluation of the presence/extent of CAD and the potential need for coronary intervention?

b. During PCI to guide stent placement?

c. Immediately after PCI to evaluate the success of stent placement?

Data Sources

We conducted literature searches for studies in MEDLINE® (through August 2012) and the Cochrane Central Register of Controlled Trials (through the 2nd quarter of 2012). Studies published in any language with adult human subjects were screened to identify articles relevant to each Key Question. We also screened the reference lists of selected narrative reviews and primary articles for additional studies. We retrieved and screened relevant abstracts from professional conferences and meetings that were available online (through June 2012) from the following resources: Transcatheter Cardiovascular Therapeutics (www.tctmd.com), the American Heart Association (www.aha.org), and the American College of Cardiology (www.cardiosource.com). We also searched the ClinicalTrials.gov Web site to identify ongoing trials.

Eligibility Criteria

We included studies conducted in adults (aged ≥18 years) with CAD who were undergoing coronary artery stenting. All forms of CAD and its clinical presentation were included. For all Key Questions, we included any intravascular diagnostic technique that evaluated morphological or physiological parameters of coronary lesions and is presently employed in clinical practice in the United States. These included IVUS, FFR, and other techniques that are primarily investigational, such as IVUS-virtual histology, OCT, elastography, NIRS, thermography, angioscopy, intravascular MRI, and techniques measuring stenosis index and index of microcirculatory resistance.

For Key Question 5, the modifiers of treatment effect of interest included patient and physician characteristics, availability of prior noninvasive testing, and the type of PCI performed. Coronary angiography alone was the comparison of interest for Key Questions 1, 2, 3, and 5. For Key Questions 4 and 5, head-to-head comparisons of two or more intravascular diagnostic techniques were included. The outcomes of interest were categorized as therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes. Outcomes were measured at three time points: short term (≤30 days after the procedure), medium term (>30 days to 1 year), and long term (>1 year).

We excluded studies that solely compared stenting with medical therapy. We also excluded studies that only compared different thresholds within a single intravascular diagnostic technique.

Outcomes

We analyzed the following three outcomes.

Therapeutic Decisionmaking

- Key Question 1: In patients with CAD, a change in the number of hemodynamically significant lesions after the application of intravascular diagnostic techniques, and the change in the decision about an interventional therapy (e.g., if stenting is needed) after the application of the intravascular diagnostic techniques
- Key Question 2: During PCI, a change in the type of stent, number of stents, or length of stent after the application of intravascular diagnostic techniques
- Key Question 3: Immediately after PCI, a change in the decision about the need for additional interventions or modifications to stent placement

Intermediate Outcomes

- Process outcomes (technical success rates assessed by quantitative coronary angiography [QCA], such as proportion of successfully completed procedures or proportion of interpretable results in completed procedures, total procedural time, fluoroscopy time, and volume of contrast medium used)
- Periprocedural complications (e.g., vessel dissection, bleeding, repeat PCI, unplanned coronary bypass surgery, and length of hospital stay)
- Resource utilization (e.g., number of guide catheters, wires, balloons, and stents)
- Stent-related complications (e.g., restenosis, stent thrombosis, and dissection)
- Other measures (e.g., findings of cardiac imaging [such as ventricular function or myocardial perfusion], electrocardiographic ischemia, biochemical markers, noninvasive assessment using magnetic resonance imaging, and a high-intensity signal on Doppler flow wire during PCI)

Patient-Centered Outcomes

- Clinical outcomes that directly affect patient well-being or clinical status (e.g., death, acute MI, repeat revascularization, composite endpoint of major adverse cardiac events [MACE], freedom from angina, quality of life, and quality-adjusted survival)

Sample Size and Study Design

We did not specify a minimum sample-size threshold or a minimum duration of followup. We included all comparative studies, including randomized controlled trials (RCTs) and nonrandomized comparative studies that provided data directly comparing intravascular diagnostic techniques and angiography with angiography alone, or studies comparing one intravascular diagnostic technique with another. We excluded narrative reviews and case reports.

Data Extraction

Each study extraction was conducted by one investigator and reviewed by at least one other investigator. Any disagreements were resolved by discussion in team meetings. We extracted basic demographic (such as age, sex, race), comorbiditiy (such as diabetes, hypertension), clinical characteristic (such as percent ejection fraction, location of stenosis, lesion type), and modifying factor data associated with the application of intravascular diagnostics and outcomes.

Data Synthesis

To evaluate the effect of an intervention on outcomes, we performed DerSimonian and Laird random effects model meta-analyses of binary data, or continuous outcomes. Meta-analyses were performed where studies included had sufficiently similar populations, had the same comparison of interventions, and the same outcomes. For each specific outcome of interest, we performed separate meta-analyses at prespecified time points. When possible, we evaluated the net change of continuous outcomes (the difference between the intervention of interest and the control intervention in terms of changes between final and baseline values). However, a large number of studies did not report full statistical analyses of the net change. Where sufficient data were reported, we calculated the net change values and estimated their standard error from reported standard deviations (or standard errors) of baseline and final values. When necessary, we arbitrarily assumed a 50 percent correlation ($r=0.5$) between baseline and final values. For outcomes that were reported as final measurements only, we conducted the weighted mean difference meta-analyses between final measurements. For each meta-analysis, the statistical heterogeneity was assessed with the I^2 statistic, which describes the percentage of variation across studies that is due to heterogeneity rather than chance. We performed sensitivity meta-analyses by excluding studies that were rated as being at a high risk of bias (see risk of bias section) to see if these studies impacted inferences

drawn from syntheses of studies with low and medium risk of bias only. We did not conduct statistical tests to assess publication bias, as most of the statistical methods for detecting or correcting for publication biases have specific drawbacks. We attempted to mitigate the issue by searching grey literature sources available online (through June 2012) from www.tctmd.com, www.aha.org, and www.cardiosource.com.

Risk of Bias

We assessed the risk of bias (methodological quality) for each study using the assessment instrument detailed by AHRQ in its "Methods Guide for Effectiveness and Comparative Effectiveness Reviews," hereafter referred to as "Methods Guide."[4] Briefly, we rated each study as being at a high, medium, or low risk of bias on the basis of their adherence to well-accepted standard methodologies for studies, including the Cochrane risk of bias tool for intervention studies, and assessed and reported each methodological quality item for all qualifying studies (yes, no, or unclear/not reported). The overall judgment of risk of bias was based on the overall study conduct, specifically relating to selection, performance, attrition, detection, and selective outcome reporting biases. Two independent reviewers evaluated the risk of bias for each study, and all disagreements were resolved in consensus with a third reviewer.

Grading the Body of Evidence

We followed the Methods Guide to evaluate the strength of the body of evidence for each Key Question with respect to four domains: risk of bias, consistency, directness, and precision. We assessed the consistency of the data as either "no inconsistency" or "inconsistency present" (or "not applicable" if only one study). The direction, magnitude, and statistical significance of all studies were evaluated in assessing consistency. We also assessed the precision and sparseness of the evidence. We considered evidence to be sparse if only one study of a small sample size addressed the analysis. Because this review assessed many outcomes within the categories of therapeutic decisionmaking, intermediate outcomes, and patient-centered clinical outcomes, we assessed the strength of evidence based on these three broad categories. However, the overall strength of evidence evaluation was based on patient-centered clinical outcomes, which were defined as any outcome that affected the patient's well-being, such as survival, MI, and quality of life.

We rated the strength of evidence (as per the Methods Guide) as high, moderate, low, or insufficient. Ratings were assigned based on our level of confidence that the evidence reflected the true effect for the major comparisons of interest. The individual ratings were defined as follows:

- **High:** There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. No important scientific disagreement exists across studies.
- **Moderate:** There is moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. Little disagreement exists across studies.
- **Low:** There is low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. Underlying studies may report conflicting results.
- **Insufficient:** Evidence is either unavailable or does not permit a conclusion. There are sparse or no data. In general, the evidence is considered insufficient when only one study has been published, unless the study was particularly large, robust, and of good quality.

Studies rated as being at a low or medium risk of bias were used in the appraisal of the strength of evidence. These ratings provide a shorthand description of the strength of evidence supporting the major questions we addressed. However, by necessity, they may oversimplify the complex issues involved in the appraisal of a body of evidence. Individual studies evaluated in formulating the composite rating differed in their design, reporting, and quality. The strengths and weaknesses of the individual reports, as described in detail in the text and tables, should also be taken into consideration.

Results

Our literature search yielded 4,023 citations. From these, 568 articles were retrieved for further evaluation on the basis of the abstracts and titles. After full-text evaluation, 37 studies, published in 42 articles, met the inclusion criteria. A grey-literature search yielded no additional eligible studies. The most common reason for article rejection was that there were no direct comparisons between intravascular diagnostic techniques and angiography (278 articles). The other reasons for rejection included ineligible publication types, such as reviews or case reports (83 articles); irrelevant comparators (e.g., intravascular diagnostic techniques compared with cardiac computed tomography; 56 articles); failing to address the Key Questions (46 articles); irrelevant

outcomes (34 articles); no intravascular diagnostic techniques used (9 articles); irrelevant or incomplete measurement time points (e.g., comparison between intravascular diagnostic techniques and angiography only at followup; 9 articles); within diagnostic technique comparisons (e.g. comparison between different criteria of the same diagnostic technique; 7 articles); and no population of interest (4 articles). The 37 studies (published in 42 articles) had data addressing at least one of the five Key Questions, and evaluated IVUS and FFR. No comparative studies were available for techniques other than IVUS and FFR.

Key Question 1: In patients with CAD, what is the impact of using an intravascular diagnostic technique and angiography in deciding whether a coronary lesion requires intervention—when compared with angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Summary of Evidence

Our appraisal of the strength of evidence relied only on studies rated as being at a low or medium risk of bias (details of the one high risk of bias study are provided in the full report). Overall, there is a moderate strength of evidence (drawn from one RCT with low risk of bias and one nonrandomized study with medium risk of bias) favoring the use of FFR during angiography in deciding whether to stent an intermediate coronary lesion (50% to 70% stenosis), using an FFR threshold <0.80. The use of FFR to decide whether to stent led to fewer stents being implanted, reduced the costs of the procedure, and conferred a lower risk for the composite endpoint of death or MI, or of MACE. The evidence was derived from studies that focused on men with lower grade angina, and excluded patients with left main disease or acute MI. Therefore, the use of FFR to decide which lesions require stenting is most applicable in patients with stable multivessel disease and intermediate coronary stenosis, excluding left main disease and acute MI.

For therapeutic decisionmaking, there is a moderate strength of evidence that the use of FFR during angiography aids in deciding whether to stent a coronary lesion, and which coronary vessels to stent, as compared with angiography alone. For intermediate outcomes, there is a moderate strength of evidence that the use of FFR reduces resource utilization in the short term (≤30 days after the procedure), as compared with angiography alone, and insufficient evidence for stent-related outcomes at any time point. For patient-centered outcomes, there is a moderate strength of evidence that the use of FFR, as compared with angiography alone, improves combined clinical endpoints (e.g., death or MI, or MACE) in the medium term (>30 days to 1 year) and long term (>1 year).

There is insufficient evidence regarding the use of any intravascular diagnostic techniques other than FFR to address Key Question 1, as none of the included studies reviewed other techniques.

Available Evidence

Three studies—including one RCT (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation [FAME] trial in three publications)[5-7] rated as being at a low risk of bias, and two nonrandomized studies (one rated as being at a medium risk of bias and the other at a high risk of bias)—reported data comparing FFR with angiography alone in patients undergoing coronary stenting. Two related RCTs in this field were excluded for the following reasons: the DEFER trial examined appropriateness of stenting a functionally nonsignificant stenosis, and did not compare FFR-guided stenting versus stenting guided by angiography alone; and in the FAME II trial, all patients underwent FFR during angiography, and FFR-guided stenting plus optimal medical therapy was compared with optimal medical therapy only.

Therapeutic Decisionmaking

FFR was found to alter therapeutic decisionmaking as compared with angiography alone. The decision whether to stent a coronary lesion during PCI, or of what type of PCI to use, was made on the basis of an FFR threshold, though the threshold used varied considerably across the three studies. Among patients referred for revascularization, stent implantation was conducted in 874 of the 1,387 lesions (63%) with an FFR of ≤0.8 in the FAME trial. No stents were placed in the remaining 513 lesions (37%) with FFR >0.8 in patients with stable multivessel coronary disease. But stenting was performed for all lesions in the angiography alone group.

The prospective, nonrandomized, comparative study found that in the FFR group, stenting was deferred in 75 of the 128 vessels (58%, with an average FFR of 0.86; the remaining 53 vessels (with an average FFR of 0.67) underwent stenting in patients with stable multivessel coronary disease. In the high risk of bias, nonrandomized comparative study, stent implantation was performed in patients with acute MI in 40 lesions (FFR <0.94), and the remaining 37 lesions (FFR ≥0.94) underwent direct

angioplasty without stenting. Similar information was not reported for the angiography alone group.

Intermediate Outcomes

Intermediate resource utilization outcomes were significantly lower in the FFR group than in the angiography alone group in the FAME trial, including for contrast use (272 vs. 302 mL; p<0.001), number of stents implanted per patient (1.9 vs. 2.7; p<0.001), and number of hospital days (3.4 vs. 3.7; p=0.05). There were no significant differences in average procedure time between the groups, although a significantly lower number of stents were implanted per patient in the FFR group than in the angiography alone group (1.9 vs. 2.7; p<0.001).

Only one of the two nonrandomized studies reported this outcome; in this study, no significant differences were found between groups in average procedure time, contrast use, and radiation exposure time. The number of stents implanted per patient was significantly lower in the FFR group than in the angiography alone group (1.04 vs. 1.28; p=0.05), in agreement with the FAME trial results. None of the nonrandomized comparative studies reported data on hospital days or data on medication use during the procedure. The cost of the procedure, including materials used during PCI, was reported in all three studies, and was significantly lower with FFR-guided stenting, compared with stent placement guided by angiography alone.

Intermediate outcomes, as measured by QCA, were reported in the two nonrandomized comparative studies at short-term followup, but not in the FAME trial. Both observational studies reported net changes in minimal lumen diameter (MLD) and percent diameter stenosis, comparing the FFR and angiography alone groups from baseline to postprocedure. The medium risk of bias study reported no significant differences in either measurement between the two groups (MLD net difference 0.02 mm, not significant (NS); diameter stenosis net difference 1%, NS). The high risk of bias study (with a historical control) reported worsening of QCA outcomes in the FFR group, compared with the angiography alone group (MLD net difference -0.3 mm, p<0.001; diameter stenosis net difference 9%, p<0.001).

Only the high risk of bias, prospective, nonrandomized, comparative study (with a historical control) reported stent-related intermediate outcomes. The study found nonsignificant higher rates of reocclusion and restenosis in the FFR group, compared with the angiography alone group. None of the included studies reported data on stent thrombosis.

Patient-Centered Outcomes

Short-term (≤ 30 days after the procedure), patient-centered outcomes in the FAME trial included periprocedural MI (2.4% in the FFR group vs. 3.2% in the angiography alone group) and MACE at hospital discharge (absolute mean difference of -2.2%). The statistical significance of both outcomes was not reported. Both nonrandomized studies reported nonsignificant differences for in-hospital clinical outcomes of MI and MACE. There were no incidences of in-hospital complications of coronary artery bypass grafting (CABG) or death reported in either of the nonrandomized studies. One nonrandomized study reported no statistical difference between groups in repeat target lesion revascularization during in-hospital stay.

All three studies reported no significant mortality differences between groups in either the medium term (>30 days to 1 year) or long term (>1 year). In the FAME trial, there was no significant difference in MI between groups at 1 year, but at 2 years there was a significant decrease in the risk of MI in the FFR group (relative risk [RR]: 0.62, 95% confidence interval [CI]: 0.40 to 0.95). The FFR group also displayed a significant decrease in the composite outcome of death and MI at both 1 and 2 years (RR: 0.66, 95% CI: 0.44 to 0.98 at 1 year, and RR: 0.65, 95% CI: 0.45 to 0.94 at 2 years). For repeat revascularization, defined as CABG or repeat PCI, a favorable effect in the FFR group did not reach statistical significance (RR: 0.68, 95% CI: 0.40 to 1.05 at 1 year; RR: 0.84, 95% CI: 0.59 to 1.18 at 2 years). While the FAME trial significantly favored FFR (RR: 0.72, 95% CI: 0.54 to 0.96) for the primary outcome of MACE—defined as death, MI, and repeat revascularization—at 1 year, this did not remain statistically significant at 2 years (RR: 0.80, 95% CI: 0.62 to 1.02).

The medium risk of bias, prospective, nonrandomized study found no significant difference in MI between groups after more than 2 years. For the composite outcome of MACE (defined as death, MI, and target lesion revascularization) in this study, significant results favored FFR over angiography after more than 2 years (8% in FFR vs. 27% in angiography alone; p<0.01). The high risk of bias, prospective, nonrandomized, comparative study did not report clinical outcomes other than death.

Other Outcomes

In the FAME trial, the average overall costs at 1 year were significantly less in the FFR group, as compared with the angiography alone group ($14,315 vs. $16,700; p<0.001).

The trial reported the European Quality of Life-5 Dimensions (EQ-5D) score at 1 year followup. There was no significant difference in EQ-5D between groups (66.5 in the FFR group vs. 64.7 in the angiography alone group). A nonsignificantly higher proportion of patients in the FFR group were event free from angina, compared with the angiography alone group (73% vs. 68%).

Key Question 2: For patients undergoing PCI, what is the impact of using an intravascular diagnostic technique and angiography to guide stent placement (either immediately prior to or during the procedure)—when compared with angiography alone—on the therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Of the 32 eligible studies that looked at optimizing stent placement (i.e., stent size and dilation) 31 involved IVUS. Only one prospective nonrandomized study (with a historical comparator; rated as being at a high risk of bias) reported data comparing FFR with angiography alone for additional therapy (dilation) after stent deployment. No studies involving techniques other than IVUS or FFR addressed Key Question 2.

IVUS Versus Angiography Alone for Guiding Stent Deployment

Summary of Evidence

Overall, there is a moderate strength of evidence that supports a reduction in repeat revascularization and restenosis, but no significant differences in mortality or MI, when using IVUS to guide stent deployment, as compared with angiography alone. The evidence was derived mostly from studies conducted before 2000 that focused on men, excluded patients with left main disease and acute MI, and used a previous generation of bare-metal stents, all of which limited the applicability of these studies. For therapeutic decisionmaking, there is a moderate strength of evidence that the use of IVUS during PCI can aid the operator in optimizing stent deployment, as compared with angiography alone. For intermediate outcomes, there is a moderate strength of evidence that the use of IVUS during PCI to optimize stent deployment increases resource utilization in the short term (≤30 days after procedure), provides no differences in QCA outcomes in the short and medium term, and lowers the risk of stent-related outcome of restenosis in the medium term (>30 days to 1 year), as compared with angiography alone. For patient-centered clinical outcomes, there is a moderate strength of evidence that there is no difference in mortality, MI, and MACE—but there is a benefit in decreasing repeat revascularizations—when using IVUS to guide bare-metal stent deployment, as compared with angiography alone.

Available Evidence

We identified 9 RCTs (11 publications) and 22 nonrandomized studies comparing IVUS-guided stent placement and stent placement guided by angiography alone.

Therapeutic Decisionmaking

Three RCTs and three nonrandomized, comparative studies reported data on changes in decisionmaking resulting from the use of IVUS in optimizing stent placement. In the RCTs, IVUS guidance in decisionmaking aided in a significantly higher proportion of patients achieving optimal stent placement (82% in the IVUS group vs. 71% in the angiography alone group; $p<0.0001$); almost one-half of the patients received further therapy for an underexpanded stent and repeat balloon angioplasty (46%); and more than one-third of patients underwent additional dilation due to not reaching the IVUS criterion (no similar data were provided for the angiography alone group).

Similar results regarding decisionmaking were reported in three nonrandomized comparative studies of IVUS-guided optimized stent deployment, which included data on additional postdilation, debulking, angioplasty, and second stent deployment.

Intermediate Outcomes

Resource utilization (including procedural time, fluoroscopy time, use of contrast medium, use of glycoprotein IIb/IIIa inhibitor, and utilization of other resources) in the short-term was reported in six RCTs and five nonrandomized, comparative studies. Overall, procedural time was significantly longer, and fluoroscopy time and the use of contrast medium was increased with IVUS-guided stent placement, as compared with angiography-guided stent placement. Generally, there were no significant differences between groups for periprocedural complications or stent-related complications, but the IVUS group had a nonsignificantly higher use of glycoprotein IIb/IIIa inhibitors during the procedure or a utilization of other resources, including guidewires, stents, and balloons.

Meta-analysis of four RCTs revealed a nonsignificant increase in the use of glycoprotein IIb/IIIa inhibitors in the IVUS-guided stenting group, compared with the

stenting guided by angiography alone group (summary RR: 1.27, 95% CI: 0.76 to 2.12).

Meta-analyses of QCA outcomes in the short term, including procedural MLD, reference vessel diameter, and percent diameter stenosis revealed nonsignificant results across RCTs and nonrandomized comparative studies (Table A). Some studies reported QCA process outcomes by lesion, while others reported QCA process by patients, complicating synthesis. Meta-analyses of QCA outcomes in the medium term—including MLD, diameter stenosis,

Table A. Summary of QCA measures comparing IVUS-guided stent placement with angiography-guided stent placement

Outcomes	Time Points	Number of RCTs (Number of Participants)	Summary of Mean Difference (95% CI)	Number of Nonrandomized Comparative Studies (Number of Participants)	Summary of Mean Difference (95% CI)
Minimal lumen diameter (mm)[†]	In-hospital (by patient)	6 (1,694)	0.09 (0, 0.19)	7 (4,330)[a]	0.07 (0.01, 0.12)[*]
	In-hospital (by lesion)	3 (659)	0.18 (-0.05, 0.42)	7 (1,592)[a]	0.29 (0.16, 0.43)[*]
	Medium term (by patient)	4 (1,025)	0.16 (0.06, 0.26)[*]	2 (339)	-0.04 (-0.30, 0.22)
	Medium term (by lesion)	0		4 (820)[b]	0.26 (-0.02, 0.54)
	Long term	Not reported		Not reported	
Diameter stenosis (%)	In-hospital (by patient)	5 (894)	-3.9 (-5.86, -1.94)[*]	7 (14,565)[a]	-1.04 (-2.04, -0.04)[*]
	In-hospital (by lesion)	3 (659)	-5.39 (-12.45, 1.67)	7 (2,972)[a]	-2.90 (-6.28, 0.49)
	Medium term (by patient)	4 (1,025)	-3.46 (-7.47, 0.55)	1 (212)	-6.00 (-11.49, -0.51)[*]
	Medium term (by lesion)	0		4 (820)[b]	-6.60 (-13.94, 0.74)
	Long term	0		0	
Reference vessel diameter (mm)[†]	In-hospital (by patient)	2 (307)	0.09 (-0.04, 0.22)	4 (3,692)	0.04 (-0.03, 0.10)
	In-hospital (by lesion)	2 (612)	0.02 (-0.06, 0.10)	5 (1,388)[c]	0.07 (0.01, 0.03)[*]
	Medium term (by patient)	3 (870)	0.11 (-0.08, 0.30)	1 (212)	0.03 (-0,13, 0.19)
	Medium term (by lesion)	0		3 (751)[d]	0.08 (-0.04, 0.20)
	Long term	0		0	

CI = confidence interval; IVUS = intravascular ultrasound; QCA = quantitative coronary angiography; RCT = randomized controlled trial

[*]Indicates statistical significance.

[†]For minimal lumen diameter and reference vessel diameter, estimates with positive differences favor IVUS use over angiography alone. For diameter stenosis, estimates with negative differences favor IVUS use over angiography alone.

[a]Seven studies provided eight data points for analysis.

[b]Four studies provided five data points for analysis.

[c]Five studies provided six data points for analysis.

[d]Three studies provided four data points for analysis.

reference diameter, and late loss—found no statistically significant difference between groups (Table A).

At short term, in-stent restenosis was not significantly different between groups in one RCT and two nonrandomized comparative studies. Two nonrandomized comparative studies reported data on subacute stent thrombosis; one reported no instance of subacute stent thrombosis, while the other reported no statistically significant difference between groups.

At medium term, meta-analysis of six RCTs revealed a significant 29 percent lower risk of restenosis in the IVUS-guided group, as compared with the angiography-guided group (summary RR: 0.71, 95% CI: 0.52 to 0.96). Meta-analysis of five nonrandomized studies revealed a similar point estimate (summary RR: 0.71, 95% CI: 0.47 to 1.09), but this finding did not reach statistical significance.

At medium term, two RCTs, and at long term, one RCT, reported no significant difference in stent thrombosis rates between groups. Meta-analysis of three nonrandomized studies found a significant decrease in the medium term (summary RR: 0.60, 95% CI: 0.42 to 0.86); however, in meta-analysis of four nonrandomized studies, this significance was lost after 2 years (summary RR: 0.75, 95% CI: 0.37 to 1.53).

Clinical Outcomes

Either no events occurred or no statistically significant differences in the risk between stenting guided by IVUS or angiography alone were observed in in-hospital clinical outcomes, including mortality, MI, and repeat revascularization (Table B).

For the medium term (>30 days to 1 year), both RCTs and nonrandomized studies reported no significant difference

Table B. Summary of clinical outcomes comparing IVUS-guided stent placement with angiography-guided stent placement

Outcomes	Time Points	Number of RCTs (Number of Participants	Summary of Relative Risk† (95% CI)	Number of Nonrandomized Comparative Studies (Number of Participants)	Summary of Relative Risk† (95% CI)
All-cause mortality	In-hospital	3 (925)	No events (3 RCTs)	2 (1,802)	No events (1 study) No statistical significance (1 study)
	Medium term	5 (1,652)	1.84 (0.88, 3.85)	8 (21,489)	0.77 (0.59, 1.00)
	Long term	3 (587)	1.06 (0.38, 2.94)	3 (5,690)	0.53 (0.34, 0.83)
MI	In-hospital	3 (925)	No event (1 RCT) No statistical significance (2 RCTs)	3 (2,227)	Favorable with IVUS (1 study) No statistical significance (2 studies)
	Medium term	4 (1,508)	0.66 (0.28, 1.56)	9 (20,311)	1.00 (0.69, 1.47)
	Long term	3 (587)	0.37 (0.09, 1.50)	5 (7,770)	0.76 (0.42, 1.36)
Repeat revascu-larization‡	In-hospital	5 (1,238)	0.50 (0.20, 1.27)	3 (212)	No events (2 studies) No statistical significance (1 study)
	Medium term	6 (1,760)	0.70 (0.51, 0.97)*	11 (22,113)	0.81 (0.65, 1.01)
	Long term	3 (587)	0.67 (0.50, 0.90)*	5 (7,700)	0.84 (0.57, 1.25)
Major adverse cardiac events	In-hospital	2 (694)	(No statistical significance (2 RCTs)	4 (7,328)	No statistical significance (4 studies)
	Medium term	5 (1,652)	0.79 (0.57, 1.11)	8 (21,268)	0.94 (0.80, 1.11)
	Long term	3 (587)	0.77 (0.58, 1.01)	6 (7,185)	0.91 (0.75, 1.09)

CI = confidence interval; IVUS = intravascular ultrasound; MI = myocardial infarction; RCT = randomized controlled trial

*Indicates statistical significance.

†A relative risk <1 indicates a favorable effect with IVUS use.

‡Clinically-driven repeat percutaneous coronary intervention or coronary bypass grafting.

between IVUS-guided stent placement and stent placement guided by angiography alone for all-cause mortality, cardiac mortality, MI, and MACE. Meta-analyses of RCTs yielded an increased risk without significant differences in mortality, but meta-analysis of nonrandomized studies found a borderline significant 23 percent reduction in mortality with IVUS use (Table B). Meta-analyses of clinically-driven repeat revascularization favored IVUS. Meta-analysis of six RCTs, enrolling almost 1,800 patients, found a significantly 30 percent lower risk of repeat revascularizations among patients who received IVUS-guided stenting, compared with those who received angiography-guided stenting. Meta-analysis of eight nonrandomized studies (enrolling almost 13,000 patients) found a smaller and marginally nonsignificant 19 percent lower risk of repeat revascularization.

With respect to the long-term data (>1 year), three RCTs found no significant difference in all-cause mortality by meta-analysis, but three nonrandomized studies found a significant 47 percent reduction in mortality with IVUS use (Table B). Both RCTs and nonrandomized studies were in agreement, finding no significant difference between the IVUS and angiography alone groups for MI and MACE (Table B). Meta-analysis of the three RCTs found a 33 percent lower risk of repeat revascularization with IVUS-guided stent placement. Meta-analysis of the five nonrandomized studies found a similar but nonsignificant effect on repeat revascularization favoring IVUS.

Other Intravascular Diagnostic Techniques Compared With Angiography Alone

There is insufficient evidence to answer Key Question 2 for all techniques other than IVUS. One high risk of bias, prospective, nonrandomized study (with a historical comparator) compared FFR-guided additional therapy (dilation) during stent deployment with angiography-guided stenting. No firm conclusions were drawn from this single, high-risk-of-bias study. There were no comparative studies evaluating any other techniques.

Key Question 3: For patients having just undergone a PCI, what is the impact of using an intravascular diagnostic technique and angiography to evaluate the success of stent placement immediately after the procedure—when compared with angiography alone—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Summary of Evidence

There is insufficient evidence to answer this Key Question. No firm conclusions were drawn from two nonrandomized studies which were both rated as being at a high risk of bias and reported on two different types of outcomes at different time points. There were no comparative studies evaluating techniques other than IVUS.

Available Evidence

One study reported no significant differences in angiographic results either during short- or long-term followup. The other study reported no significant differences in the incidence of restenosis between the two groups.

Key Question 4: How do different intravascular diagnostic techniques compare with each other in their effects on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Summary of Evidence

There is insufficient evidence to answer this Key Question. Only one study rated as being at a high risk of bias provided relevant data comparing FFR versus IVUS. There were no comparative studies evaluating any other techniques.

Available Evidence

One nonrandomized study, rated as being at a high risk of bias, compared FFR-guided with IVUS-guided stent placement in patients with intermediate coronary lesions (40% to 70% diameter stenosis by visual assessment). The study compared FFR (cutoff 0.8) or IVUS (4 mm^2 derived minimal lumen area), and the use of FFR or IVUS was based on operator preference. Of 83 patients in the FFR group, 28 received stents (34%), while 86 of 94 patients in the IVUS group received stents (92%; $p<0.001$). The 1-year composite outcome of MACE was not significantly different between FFR and IVUS (3.6% vs. 3.2%). No firm conclusions were drawn from this single, high-risk-of-bias study.

Key Question 5: What factors (e.g., patient/physician characteristics, availability of prior noninvasive testing, type of PCI performed) influence the effect of intravascular diagnostic techniques—when compared with angiography

alone (or among different intravascular diagnostic techniques)—on therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?

Summary of Evidence

There is a moderate strength of evidence that the effect of IVUS on outcomes did not vary by factors including left main disease, sex, diabetes mellitus status, lesion length, and reference diameter. All studies addressing this Key Question evaluated IVUS only. Therefore, the strength of evidence for all other intravascular diagnostic techniques was rated insufficient. Given a lack of data, there is also insufficient evidence about additional factors of interest, including chronic inflammation (e.g., systemic lupus erythematosus) and atherosclerosis following heart transplantation.

Available Evidence

One prospective study with a medium risk of bias (9,070 patients) and one retrospective study with a high risk of bias (58 patients) evaluated factors influencing the comparative effectiveness of IVUS versus angiography. Both studies enrolled patients with CAD who presented with angina, silent ischemia, or left main disease, and who were undergoing a PCI procedure with or without stenting. Both studies used IVUS in patients during PCI or immediately after PCI, and compared them with patients whose stents were placed using angiography alone. One study compared the use of IVUS with no IVUS in a subgroup of patients with distal and nondistal left main disease. Even though presence of distal left main disease was significantly associated with adverse outcomes compared with nondistal left main disease, the rate of events did not significantly differ between the IVUS or no IVUS groups, irrespective of variations in anatomic left main disease. Evaluation of factors such as sex, diabetes mellitus status, lesion length, and reference diameter for interactions with stenting guided by IVUS or angiography alone, had no significant association with MACE or its individual components.

Discussion

Key Findings and Strength of Evidence

Our review found that eligible studies addressed only two techniques, FFR and IVUS. Comparative data with respect to angiography alone were available on the use of FFR, which measures the physiological severity of coronary stenosis to decide which coronary lesions require stenting (Key Question 1), and on the use of IVUS, which visualizes coronary anatomy to optimize stent deployment (Key Question 2). There were insufficient data concerning the use of intravascular diagnostic techniques immediately after PCI to evaluate the success of stent placement, as compared with angiography alone (Key Question 3), or for direct comparisons between intravascular diagnostic techniques (Key Question 4). Data were also available on the association (or lack thereof) between IVUS and factors such as left main disease, sex, diabetes mellitus status, and lesion length and reference diameter (Key Question 5). The summary of evidence for each Key Question is provided in Table C.

This review suggests that the use of FFR to decide which coronary lesions require intervention would confer a lower risk of the combined endpoint of death or MI, or of MACE in patients with intermediate coronary stenosis, as compared with stent placement guided by angiography alone. This finding may not hold for patients with more severe CAD. Specifically, the evidence was derived from studies that focused on men with lower grade angina, and excluded patients with left main disease and acute MI. Therefore, the use of FFR to decide which lesions require stenting is most applicable in patients with stable multivessel disease and intermediate coronary stenosis, excluding left main disease and acute MI. Additionally, this review indicates that FFR-guided stenting would decrease procedural costs and would lead to fewer stents implanted, as compared with stenting guided by angiography alone.

Based primarily on the FAME trial and one medium risk of bias, nonrandomized study, we conclude that there is moderate evidence that the use of FFR during stenting confers a lower risk of the combined endpoint of death or MI, or of MACE in patients with intermediate coronary lesions, excluding left main disease and acute MI.

This review also indicates that the use of IVUS, compared with angiography alone to guide stent deployment, achieved measureable improvements in intermediate QCA outcomes, including MLD, percent diameter stenosis, and reference vessel diameter. However, the gains achieved in intermediate outcomes with IVUS-guided stenting did not translate into significant differences in mortality or MI during followup. Nevertheless, there were significant reductions in repeat revascularization and restenosis rates during medium-term (>30 days to 1 year) or long-term (>1 year) followup with IVUS-guided stenting versus stent placement guided by angiography alone, with a reduction in repeat revascularization of about 30 percent (mostly observed in RCTs of modest sample size). The lower

Table C. Summary of evidence addressing Key Questions		
Key Question	**Strength of Evidence**	**Summary, Conclusions, and Comments**
Key Question 1 (deciding which coronary lesions need intervention)	FFR: **Moderate** (favoring FFR during medium- and long-term) Other intravascular diagnostic techniques: Insufficient	• Favorable effect for FFR-guided stenting over stent placement guided by angiography alone in intermediate coronary lesions (based on one RCT that defined intermediate lesions as those 50% to 70% stenosis) for improved patient-centered outcomes in studies that focused on men with intermediate coronary disease and lower grade angina, and excluded patients with left main disease and acute MI. • No studies compared the use of other intravascular diagnostic techniques besides FFR.
Key Question 2 (guiding PCI and deployment of stent and optimization)	IVUS: **Moderate** (favoring IVUS with reduction in repeat revascularization* and restenosis, but none for mortality* or MI) Other intravascular diagnostic techniques: Insufficient	• Favorable effect for IVUS-guided stent deployment over stenting guided by angiography alone for reduction of clinically-driven repeat revascularization and restenosis in studies conducted before 2000 that focused on men, excluded patients with left main disease and acute MI, and used previous generation bare-metal stents. • No studies compared the use of other intravascular diagnostic techniques besides IVUS.
Key Question 3	All intravascular diagnostic techniques: **Insufficient**	• Two small retrospective studies addressed Key Question 3. One compared the use of IVUS with angiography in patients who had a stand-alone DCA. No significant differences in angiographic results were observed up to a mean of 5.7 years of followup. The other study compared the use of IVUS after PTCA with PTCA without IVUS. Some differences in incidence of restenosis were observed at 3 to 6 months. However, no statistical comparison was reported, making the results difficult to interpret.
Key Question 4	All intravascular diagnostic techniques: **Insufficient**	• One small retrospective study compared FFR-guided PCI with IVUS-guided PCI in patients with intermediate coronary lesions. The 1-year composite outcome of death, MI, and ischemia-driven target vessel revascularization was not significantly different between FFR and IVUS.
Key Question 5	IVUS: **Moderate** (no association) Other intravascular diagnostic techniques: Insufficient	• Two studies evaluated patient subgroups of IVUS- or angiography-guided PCI and found no association between factors including sex, diabetes mellitus status, lesion length and reference diameter, left main disease, and individual components or composite outcomes of MACE.

CI = confidence interval; IVUS = intravascular ultrasound; MI = myocardial infarction; RCT = randomized controlled trial
*Indicates statistical significance.
†A relative risk <1 indicates a favorable effect with IVUS use.
‡Clinically-driven repeat percutaneous coronary intervention or coronary bypass grafting.

repeat revascularization and restenosis rates reported with IVUS-guided stenting should be interpreted cautiously as these studies were conducted using a previous generation of bare-metal stents, and the results may no longer be applicable to current clinical practice with a widespread use of drug-eluting stents and other newer stents.

IVUS-guided stenting appears to be associated with longer procedural times, greater radiation exposure, and greater contrast use than angiography-guided stenting, all factors that may be associated with short- and long-term complication risks.

Context of Findings

Our review concurs with three recently published systematic reviews comparing the effect of IVUS-guided PCI and non-IVUS-guided PCI, which found no

significant differences between groups for the clinical outcomes of mortality or MI, but found a significant difference in target vessel revascularization in randomized trials favoring IVUS-guided PCI over non-IVUS-guided PCI.[8-10] While the reviews also found a significant decrease in MACE with the use of IVUS-guided PCI compared with non-IVUS-guided PCI,[8-10] our review, which included additional studies from recent literature, did not. The disparity in our findings could be explained by the differences in eligibility criteria, in the number of included studies, or the methods of analyses. The first review searched until 1999, but only two RCTs overlapped with our review because of differences in eligibility criteria;[8] the second review searched until 2001, and identified five of the total nine RCTs included in our review;[9] and the third review combined medium- and long-term data, which found statistically significant results for MACE.[10]

In this review, we examine both older studies (examining PCI with bare-metal stents) and more recent studies (examining PCI with drug-eluting stents). This review also comprehensively evaluates nonrandomized comparative studies of intravascular diagnostic techniques. Our analyses evaluate both intermediate and clinical outcomes at various time points (short, medium, and long term). Such extensive assessments have not been carried out by prior reviews, which most often evaluated only the last reported time point. Also, in contrast to prior reviews, we examined the impact of FFR in both RCTs and nonrandomized studies conducted in real-world settings, and found consistent results. In addition, our review synthesizes data and analyzes gaps in the literature on the use of intravascular diagnostic techniques at various stages of stenting (before, during, and after), and evaluates the role of these techniques in therapeutic decisionmaking. In summary, our review comprehensively examines both IVUS and FFR data, and has identified a lack of comparative studies for emerging novel and hybrid techniques.

Applicability

Reviewed studies were conducted in tertiary care centers and were carried out mostly in Western Europe and North America. The majority of the patients in these studies were men, and the reviewed studies specifically excluded individuals with left main disease or acute MI. Minorities were underrepresented, although a few studies reported baseline data by race or ethnicity. These eligibility criteria likely selected groups of patients with intermediate coronary stenosis, better functional status, and higher socioeconomic status (which is inversely associated with severity of CAD[11]), thus limiting applicability in patients with severe CAD. Most IVUS trials (seven of nine RCTs) reviewed were performed before 2000. Interventional techniques and technology have evolved considerably since then, not only in terms of high-pressure balloon inflation, but also in stent design, composition, delivery systems, balloon technology, adjunctive pharmacotherapy, and other features. Current bare-metal stents are radically different than those used before 2000; and only two RCTs evaluated IVUS-guided stent placement in patients with a drug-eluting stent, and none evaluated second-generation drug-eluting stents or bioabsorbable stents. Thus, overall, there are several important groups of patients who have not been adequately represented in the available literature.

Implications for Clinical and Policy Decisionmaking

There is a moderate strength of evidence favoring FFR-guided stenting over stent placement guided by angiography alone, in patients with intermediate coronary lesions; these findings are supported by only one large trial (FAME)[5-7] and one nonrandomized study. Although the evidence was rated to be of moderate strength, there is the possibility that future studies will not support the favorable effect of FFR-guided stenting. The phenomenon of an initial effect eventually dissipating through subsequent studies has been well documented elsewhere.[12] It is also worth noting that the FAME trial included patients with intermediate stenosis and lower grades of angina. The intrinsic risk of nonischemic stenosis may be lower than the risk of stent implantation itself. Treating low-risk lesions could lead to additional invasive tests or treatments that could adversely impact long-term clinical outcomes. Therefore, the use of stents in treating low-risk lesions should be weighed against this consideration. These decisions are not always straightforward in clinical practice.

Currently, IVUS is extensively applied in certain clinical situations and specific lesion subsets (e.g., left main disease), without the backing of sufficient comparative data as evidenced in this review. Additionally, IVUS is used to assess stent apposition and adequate stent expansion, lesion coverage, and edge dissections when the operator cannot angiographically determine with certainty whether a potentially life-threatening technical complication exists (i.e., one that could lead to stent thrombosis and potentially death), despite the fact that the effectiveness of IVUS in these clinical scenarios has not been evaluated in comparative studies. IVUS cannot fully assess the physiological significance of lesions (in deciding if a coronary lesion needs intervention); therefore, operators may have to use additional techniques

to evaluate physiological stenosis, especially in nonleft main disease lesions and small coronary arteries (<3 mm minimal lumen diameter).

FFR and IVUS are often used as complementary modalities during an intervention to evaluate different aspects of CAD and to help decide on the best approach for disease management. Therefore, head-to-head comparisons of these techniques may not be possible or meaningful. Our review did not find comparative data correlating findings of OCT, IVUS-virtual histology, NIRS, or any hybrid technique with subsequent outcomes and events, or on their relative impacts and resource utilization profiles. Further research is needed to evaluate the future use of hybrid and other novel intravascular diagnostic techniques.

Intravascular diagnostic techniques are quickly evolving, and differences in their learning curves and the skill with which they are employed can potentially influence outcomes. Additional studies are necessary to determine the implications of these factors on clinical and policy decisionmaking.

Limitations

Intravascular diagnostic techniques are rapidly evolving technologies, which likely explain why we found few comparative studies except for two established techniques, IVUS and FFR. There was insufficient evidence to answer two of the five review's Key Questions. This review included only direct comparisons and studies that had two distinct comparison groups (intravascular diagnostic technique and angiography vs. angiography alone). We excluded studies that lacked a distinct group (at both intervention and followup) whose stents were placed using angiography alone. We also did not examine the impact of different thresholds for FFR, or the impact of either technology on treatment decisions besides stenting.

Other restrictions included the focus of Key Questions on the short timeframe around PCI, thereby excluding studies evaluating the intravascular diagnostic techniques during followup only (but not during PCI). The reporting of timing of intravascular diagnostic technique application in reviewed studies was often unclear (e.g., during PCI or immediately after).

Outcome reporting (primarily with respect to patient-centered outcomes) was not complete in the included studies. There was also substantial heterogeneity in definitions of the composite outcome of MACE. None of the studies included in our review were sufficiently powered to address the effectiveness of IVUS to improve long-term outcomes, and few studies reported long-term outcome data. We were not able to conduct meaningful subgroup analyses stratifying older versus newer studies (studies conducted before 2000 vs. those conducted since 2000), because of the small number of IVUS RCTs conducted since 2000.

Few studies evaluated the comparative effectiveness of these intravascular diagnostic techniques in patients undergoing drug-eluting stent implantation, specifically with the latest generation of stents. And studies often did not evaluate the effect of training of operators, and the variability in the application of these techniques on clinical outcomes. Studies did not report the effect of evolution of intravascular diagnostic techniques during the study periods.

Future Research Needs

This review has identified a number of substantial gaps in the intravascular diagnostic technique literature. First, the contemporary role of IVUS guidance in drug-eluting stent placement needs to be evaluated; second, the prognostic role of FFR should be confirmed in further trials; and third, hybrid and novel techniques need to be evaluated for comparative efficacy and safety. This review also indicates that the use of FFR needs further evaluation in patients with more severe CAD and in women with CAD.

While early studies evaluating drug-eluting stents have used IVUS during stent placement, comparative studies, particularly RCTs of drug-eluting stents placed using IVUS or angiography alone, are lacking. The potential advantage of IVUS guidance in drug-eluting and bioabsorbable stent placement requires further evaluation. IVUS continues to be used to guide stent placement in small vessels, complex lesions, and long lesions. It is important, then, that additional RCTs in these populations are conducted to assess the comparative effectiveness of IVUS in the drug-eluting stent era.

FFR and IVUS could be used beyond guiding and optimizing stent deployment—for example, FFR could be used in other revascularization options (e.g., CABG), or to identify patients with stable CAD who may benefit from stenting (e.g., patients in the FAME II trial[3]). The role of FFR in high-risk patients with bifurcation lesions, left-main coronary artery stenosis, ostial stenosis, acute coronary syndrome, or for use in side branches and other clinical situations, should be better defined in future trials. In addition, the role of FFR and IVUS needs to be better defined in other vascular territories, outside of coronary circulation. Data correlating findings of investigational, high-resolution imaging techniques, such as OCT,

IVUS-virtual histology, and NIRS, with subsequent outcomes and events are needed. Initial studies have suggested that these high-resolution imaging modalities show promise in the treatment of patients with CAD, and we await evidence which supports the comparative effectiveness of these modalities. Catheters are currently deployed in combination with multiple imaging modalities (FFR, OCT, IVUS, or others) for more comprehensive assessment, with an aim towards improving the effectiveness and efficiency of interventions. But these hybrid systems could also add to the time, risk, and resource utilization of catheterization procedures. At present, the absence of comparative data available for hybrid and novel devices limits evaluations of their effectiveness in routine clinical practice. Additionally, up and coming techniques require further evaluation, such as virtual FFR which can quantify the FFR for each lesion from the data taken noninvasively via computer analysis of coronary computed tomography angiograms or via magnetic resonance angiograms.

Future research is also needed to enrich our understanding of the comparative effectiveness of intravascular diagnostic techniques (both established and novel) and angiography in diverse populations (including by race/ethnicity and socioeconomic status), in women, and in patients with left main disease and acute MI. Studies published in the past often excluded or recruited a small proportion of these populations while evaluating established techniques such as FFR. There are no published comparative studies evaluating novel techniques. Furthermore, more studies with followup duration greater than 1 year are needed to enhance our understanding of the long-term impact of the use of intravascular diagnostic techniques.

Investigators should attempt to achieve consensus in harmonizing outcomes assessment. Studies have either reported procedural data by patients or by lesions, complicating synthesis across studies. Future research is also needed to assess the usefulness of how these procedural data are presented, for example, if data by patients are preferable over data by lesions. Until consensus is achieved, investigators should be encouraged to present data both by patients and by lesions.

Conclusions

There is a moderate strength of evidence that that the use of FFR—to decide whether intermediate coronary lesions require stenting—confers a lower risk of composite endpoint of death or MI, or of MACE, decreases costs of the procedure, and leads to fewer stents implanted, as compared with stenting decisions based on angiography alone. However these findings are based on a single RCT (the FAME trial);[5] further trials are needed to confirm and expand upon these results. There is a moderate strength of evidence that the use of IVUS to guide stent optimization reduces clinically-driven repeat revascularizations and restenosis but does not affect mortality or MI rates, as compared with angiography alone. However, most of the IVUS trials were performed before 2000. There are only two RCTs evaluating IVUS-guided, drug-eluting stent placement, and none with second generation drug-eluting stents. These factors affect the present-day applicability of the existing data. Furthermore, the majority of the eligible studies focused on men with lower grade disease, and excluded patients with left main disease. Future studies (regardless of technology or the current intervention of interest) should include a more representative proportion of women and patients with more serious CADs. Future work will also need to evaluate longer-term (on the order of years) patient outcomes to better appreciate the true impact of these techniques.

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Full Report

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