



# Effective Health Care Program

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Comparative Effectiveness Review  
Number 104

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



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

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see [www.effectivehealthcare.ahrq.gov/reference/purpose.cfm](http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm).

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We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

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

## Structured Abstract

**Background.** Several intravascular diagnostic techniques provide detailed information regarding the narrowing (stenosis) of the lumen of coronary arteries. They are increasingly used in addition to angiography during coronary artery stenting.

**Purpose.** To systematically review the comparative effectiveness of intravascular diagnostic techniques versus angiography alone in patients with coronary artery disease who are undergoing percutaneous coronary interventions for the following objectives: (a) to decide whether a coronary lesion needs to be stented; (b) to guide and optimize stent deployment; (c) to assess whether stent placement was successful; and (d) to evaluate the factors influencing the diagnostic techniques' effect on outcomes.

**Data sources.** MEDLINE<sup>®</sup>, Cochrane Central Register of Controlled Trials, recent conference proceedings, and ClinicalTrials.gov.

**Study selection.** We included studies of any design and duration of followup, without any language or sample size restriction. We excluded studies that did not directly compare the use of an intravascular diagnostic technique with angiography alone or another intravascular diagnostic technique to decide whether to stent or to guide coronary artery stenting.

**Data extraction.** We extracted details on study population characteristics and results, and assessed studies for risk of bias. We evaluated therapeutic decisionmaking outcomes, intermediate outcomes, and patient-centered outcomes. We appraised strength of evidence primarily based on studies rated as having a low or medium risk of bias.

**Data synthesis.** In total, 37 eligible studies evaluated two of the intravascular diagnostic techniques, namely fractional flow reserve (FFR) and intravascular ultrasound (IVUS). There is a moderate strength of evidence (drawn from one randomized controlled trial [RCT] and one nonrandomized study) that the use of FFR, as compared with angiography alone, supports the following: (a) FFR is effective in helping to decide whether intermediate coronary lesions (defined as 50% to 70% stenosis) require stenting; (b) FFR confers a lower risk of the composite endpoint of death or myocardial infarction (MI) or of major adverse cardiac events; and (c) FFR leads to fewer stents implanted and reduces the cost of the procedure. Regarding the comparison of IVUS-guided stenting and stent placement guided by angiography alone, there is a moderate strength of evidence (drawn from 9 RCTs and 22 nonrandomized studies) that supports no significant difference between the two approaches in mortality or MI, but a significant reduction in repeat revascularizations and restenosis with IVUS-guided stenting. There is insufficient evidence concerning the use of intravascular diagnostic techniques immediately after percutaneous coronary interventions to evaluate the success of stenting compared with angiography or for direct comparisons between intravascular diagnostic techniques. There is a moderate strength of evidence (on the basis of one large nonrandomized study) that sex, diabetes



mellitus status, lesion length, and reference diameter among those undergoing IVUS- and angiography-guided stent placement had no significant association with major adverse cardiac events or its individual components. There is insufficient evidence to evaluate the comparative effect of intravascular diagnostic techniques other than FFR and IVUS.

**Limitations.** Studies evaluating FFR and IVUS were limited by incomplete outcome reporting, heterogeneity in outcome definitions, infrequent enrollment of women, and a lack of data on patients with left main coronary artery disease or acute MI. The evidence for FFR was derived from trials that focused on patients with lower grade angina or those with nonischemic intermediate coronary stenosis. The majority of the IVUS trials were conducted before 2000, a particularly important limitation given the rapid pace of technological advancement in this domain.

**Conclusions.** There is a moderate strength of evidence that the use of FFR (as compared with angiography alone) to decide whether or not to stent an intermediate coronary lesion confers a lower risk of composite endpoint of death or MI, or of major adverse cardiac events; leads to fewer stents being implanted; and reduces procedural costs. There is a moderate strength of evidence that the use of IVUS (as compared with angiography alone) to guide optimal stent placement reduces repeat revascularization and restenosis, but does not affect mortality or MI. Future studies will need to focus on women and on patients with more severe coronary artery disease, and to evaluate longer term (on the order of years) patient outcomes to better appreciate real world effectiveness. Stenting low-risk lesions may lead to additional invasive tests or treatments that could adversely impact long-term outcomes. Further research is also needed to evaluate the use of hybrid and novel intravascular diagnostic techniques.

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# 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.

PCI with stent deployment has traditionally been based on coronary angiography, an imaging technique for visualizing the interior of blood vessels that can be 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.<sup>1</sup> 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.<sup>2,3</sup> 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<sup>®</sup> (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](http://www.tctmd.com)), the American Heart Association ([www.aha.org](http://www.aha.org)), and the American College of Cardiology ([www.cardiosource.com](http://www.cardiosource.com)). We also searched the ClinicalTrials.gov Web site to identify ongoing trials.



## Eligibility Criteria

We included studies conducted in adults (aged  $\geq 18$  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 ( $\leq 30$  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), comorbidity (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](http://www.tctmd.com), [www.aha.org](http://www.aha.org), and [www.cardiosource.com](http://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.”<sup>4</sup> 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 ( $\leq 30$  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)<sup>5-7</sup> 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  $\leq 0.8$  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  $\geq 0.94$ ) 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 ( $\leq 30$  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 ( $\leq 30$  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, 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).



**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) <sup>†</sup>	In-hospital (by patient)	6 (1,694)	0.09 (0, 0.19)	7 (4,330) <sup>a</sup>	0.07 (0.01, 0.12) <sup>*</sup>
	In-hospital (by lesion)	3 (659)	0.18 (-0.05, 0.42)	7 (1,592) <sup>a</sup>	0.29 (0.16, 0.43) <sup>*</sup>
	Medium term (by patient)	4 (1,025)	0.16 (0.06, 0.26) <sup>*</sup>	2 (339)	-0.04 (-0.30, 0.22)
	Medium term (by lesion)	0		4 (820) <sup>b</sup>	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) <sup>*</sup>	7 (14,565) <sup>a</sup>	-1.04 (-2.04, -0.04) <sup>*</sup>
	In-hospital (by lesion)	3 (659)	-5.39 (-12.45, 1.67)	7 (2,972) <sup>a</sup>	-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) <sup>*</sup>
	Medium term (by lesion)	0		4 (820) <sup>b</sup>	-6.60 (-13.94, 0.74)
	Long-term	0		0	
Reference vessel diameter (mm) <sup>†</sup>	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) <sup>c</sup>	0.07 (0.01, 0.03) <sup>*</sup>
	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) <sup>d</sup>	0.08 (-0.04, 0.20)
	Long term	0		0	

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

<sup>\*</sup>Indicates statistical significance.

<sup>†</sup>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.

<sup>a</sup>Seven studies provided eight data points for analysis.

<sup>b</sup>Four studies provided five data points for analysis.

<sup>c</sup>Five studies provided six data points for analysis.

<sup>d</sup>Three studies provided four data points for analysis.

## 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 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.

**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 <sup>†</sup> (95% CI)	Number of Nonrandomized Comparative Studies (Number of Participants)	Summary of Relative Risk <sup>‡</sup> (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 revascularization <sup>‡</sup>	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.

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

<sup>‡</sup>Clinically-driven repeat percutaneous coronary intervention or coronary bypass grafting.

## 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<sup>2</sup> 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 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.

**Table C. Summary of evidence addressing Key Questions**

Key Question	Strength of Evidence	Summary, Conclusions, and Comments
<b>Key Question 1 (deciding which coronary lesions need intervention)</b>	FFR: <b>Moderate</b> (favoring FFR during medium- and long-term)  Other intravascular diagnostic techniques: Insufficient	<ul style="list-style-type: none"> <li>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.</li> <li>No studies compared the use of other intravascular diagnostic techniques besides FFR.</li> </ul>
<b>Key Question 2 (guiding PCI and deployment of stent and optimization)</b>	IVUS: <b>Moderate</b> (favoring IVUS with reduction in repeat revascularization* and restenosis, but none for mortality* or MI)  Other intravascular diagnostic techniques: Insufficient	<ul style="list-style-type: none"> <li>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.</li> <li>No studies compared the use of other intravascular diagnostic techniques besides IVUS.</li> </ul>
<b>Key Question 3</b>	All intravascular diagnostic techniques: <b>Insufficient</b>	<ul style="list-style-type: none"> <li>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.</li> </ul>
<b>Key Question 4</b>	All intravascular diagnostic techniques: <b>Insufficient</b>	<ul style="list-style-type: none"> <li>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.</li> </ul>
<b>Key Question 5</b>	IVUS: <b>Moderate</b> (no association)  Other intravascular diagnostic techniques: Insufficient	<ul style="list-style-type: none"> <li>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.</li> </ul>

DCA = directional coronary atherectomy; FFR = fractional flow reserve; IVUS = intravascular ultrasound; MACE = major adverse cardiac event; MI = myocardial infarction; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial

\*There were inconsistent findings between RCTs and nonrandomized studies in statistical significance for repeat revascularization and clinical significance for mortality.

## 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.<sup>8-10</sup> While the reviews also found a significant decrease in MACE with the use of IVUS-guided PCI compared with non-IVUS-guided PCI,<sup>8-10</sup> 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;<sup>8</sup> the second review searched until 2001, and identified five of the total nine RCTs included in our review;<sup>9</sup> and the third review combined medium- and long-term data, which found statistically significant results for MACE.<sup>10</sup>

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<sup>11</sup>), 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)<sup>5-7</sup> 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.<sup>12</sup> 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<sup>3</sup>). 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);<sup>5</sup> 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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# Introduction

Coronary artery disease (CAD) involves narrowing (stenosis) of one or more of the epicardial coronary arteries. It is most commonly due to a buildup of plaque (atherosclerosis), which impedes the ability of these blood vessels to deliver oxygenated blood to the heart muscle (myocardium). This form of arteriosclerosis is characterized by a hardening of the arterial walls, cholesterol deposition, local inflammation, fibrosis, and progressive narrowing (stenosis) of the lumen of these vessels.<sup>1</sup> It is a long-term health condition that affects populations with untreated or ineffectively treated risk factors, such as high blood pressure, high levels of cholesterol, diabetes, and smoking. Coronary atherosclerosis is a chronic disease with stable and unstable periods. Patients with stable angina usually experience effort-related symptoms. These symptoms arise because of an inability to augment myocardial blood flow in response to exertion, due to a fixed stenosis. During unstable periods, activated inflammation in the vascular wall may lead to atheromatous plaque rupture and thrombus formation, resulting in chest pain (unstable angina) or a heart attack (myocardial infarction [MI]).<sup>2</sup>

## Burden of Disease

Cardiovascular disease is a leading cause of morbidity and mortality worldwide, accounting for 17.3 million (30%) of all deaths globally in 2005; of these, 7.3 million were due CAD.<sup>3</sup> Although, there has been a steady decline in the age-adjusted mortality rates for CAD,<sup>4</sup> it is still the leading cause of death in the United States of both men and women. CAD is a major cause of disability and comprises a significant portion of the consumption of health care resources. In the United States alone, health care costs for management of CAD are projected to increase by 41 percent from \$126.2 billion to \$177.5 billion in 2040.<sup>5</sup> In the United States in 2010, the prevalence of CAD among men was 7.8 percent and among women was 4.6 percent. Elderly ( $\geq 65$  years of age), American Indians/Alaska natives and people with less than a high school education had the greatest prevalence of CAD that were 19.8 percent, 11.6 percent, and 9.2 percent, respectively.<sup>6</sup>

## Challenges of Diagnosing Coronary Stenoses

Treatment options for CAD vary according to the disease presentation (i.e., acute or chronic). The management of acute coronary syndrome may include the use of thrombolytics (“clot busting” medications), urgent or emergent percutaneous coronary intervention (PCI), or coronary artery bypass graft surgery (CABG) depending on clinical factors and the specific subtype (ST segment elevation and certain non-ST segment elevation syndromes, as defined by electrocardiogram). Adjunctive medical therapies in acute coronary syndromes include the use of antiplatelet and anticoagulant medications (blood thinners). For patients with stable CAD, mechanical revascularization (i.e., PCI or CABG) are indicated: 1) to improve survival in patients with high risk coronary anatomy (e.g.,  $\geq 50\%$  left main coronary artery stenosis, or  $\geq 70\%$  stenoses in three major coronary arteries); 2) to improve symptoms in patients with unacceptable lifestyle limiting angina despite aggressive medical therapy, and with one or more significant ( $\geq 70\%$  diameter) coronary artery stenoses amenable to revascularization. There are a number of details and variations of these revascularization guidelines, which are beyond the scope of the present review.<sup>7,8</sup>

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 it requires PCI or bypass grafting. If PCI is prescribed, the particulars of how to stent the lesion (stent size, length, material, and positioning) and, following the procedure, whether stenting was successful, must also be determined. PCI with stent deployment has traditionally been based on coronary angiography, an imaging technique for visualizing the interior of blood vessels that can be analyzed either qualitatively (visual inspection of the radiocontrast luminogram) or quantitatively (computer-based quantitation). While angiography is the standard technique for anatomic visualization of coronary arteries, it only visualizes an outline of the luminal wall and, generally, has limited ability in determining the functional severity of stenoses. Because the outer wall of the artery enlarges to accommodate the growing plaque (positive remodeling),<sup>9</sup> angiographic evidence of stenosis is usually not detected until the plaque approaches 40 to 50 percent of the total cross-sectional area of the coronary artery. For intermediate ranges of coronary stenoses (40% to 70%), there is considerable variability between angiographic and physiologic assessments of stenoses severity, making it difficult to determine whether stenting will be needed, as angiography often under- or overestimates lumen dimensions.<sup>10</sup> The use of angiography alone 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. In addition, angiography may not reveal the detailed morphology of complex lesions (e.g., ostial, graft, or bifurcation lesions) and lesions in left main coronary artery. Angiography also cannot provide information on the composition of the coronary plaque, which could be important in determining therapeutic choices.<sup>9</sup> In addition, it is difficult to assess by angiography alone whether a stent is 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 for the purpose of providing more detailed anatomic and hemodynamic information in coronary stenoses. Intravascular diagnostic techniques do not preclude the use of angiography; rather, they are complementary in nature by assisting treatment decisionmaking.<sup>11</sup>

One such intravascular diagnostic technique, fractional flow reserve (FFR), defined as 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.<sup>12,13</sup> Other less commonly used techniques to determine the physiological severity of coronary stenosis include coronary flow reserve (CFR) and tests that measure the stenosis index and the index of microcirculatory resistance.

Among the intravascular diagnostic techniques used to visualize coronary anatomy, intravascular ultrasound (IVUS) is the most common. IVUS augments angiography by providing precise lesion characteristics, such as minimal and maximal lumen diameters, cross-sectional area, and plaque area. Other intravascular diagnostic techniques to visualize 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).

## **Proposed Advantages of Intravascular Diagnostic Techniques**

Intravascular diagnostic techniques are potentially valuable in a number of clinical scenarios. For example, IVUS provides precise visualization of intracoronary anatomy, atherosclerotic plaque composition, and changes in vessel dimensions. It could be used in stent deployment and optimization, thereby improving long-term clinical outcomes. Conversely, FFR might help identify patients whose stenoses are not really impeding flow and thereby reduce the number of stents used and limit patient exposure to the risks of the initial or repeat revascularization procedures and antiplatelet agents.<sup>12,13</sup>

While intravascular diagnostic techniques do provide additional anatomic and hemodynamic information during PCI, they are invasive techniques, and their application can potentially result in procedure-related complications or increased procedural times and high initial costs. The use of these adjunctive invasive procedures themselves could 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 to patients that outweigh the risks. These decisions are not always straightforward. Invasive intravascular diagnostic modalities have emerged as potentially important complementary tools to angiography, as other available noninvasive imaging techniques for evaluating stenoses are inferior in a number of respects, such as having much lower resolutions than invasive techniques (e.g., cardiac computed tomography compared with IVUS).

## **Current Uncertainties About Intravascular Diagnostic Techniques**

Recent clinical practice guidelines have indicated that FFR and IVUS can be useful in certain clinical contexts—specifically, FFR in determining the necessity of stenting in angiographically borderline-significant lesions, and IVUS for providing technical guidance during PCI and optimizing stent deployment results.<sup>7,8</sup> The systematic reviews currently available do not comprehensively examine the role of intravascular diagnostic techniques in relation to the settings of interest (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 the newer drug-eluting stents). Furthermore, variation in how intravascular diagnostic techniques are adopted in clinical practice across catheterization laboratories reflects considerable uncertainty regarding the utility and role of these techniques.<sup>14</sup> Thus, a Comparative Effectiveness Review on the use of intravascular diagnostic applications in patients with CAD is timely and necessary to assess the clinical impact of incorporating such techniques into coronary revascularization procedures.

## **Narrative Description of Intravascular Diagnostic Techniques**

### **Reference Diagnostic Technique: Angiography**

Angiography is the current reference standard for identifying coronary artery lesions. It provides 2-dimensional silhouette image information about the luminal diameter and enables visualization of the luminal surface to diagnose atherosclerotic disease. The stenosis severity by angiography is reported as a ratio of the stenosis' minimal lumen diameter (MLD) to the adjacent

“normal” reference segment. Computer-assisted, automated, edge-detection algorithm systems are often used to quantify coronary stenoses more accurately (e.g., quantitative coronary angiography [QCA]). Angiography may underestimate the degree of stenosis or atheroma burden, particularly in the setting of diffuse CAD, or because of the positive remodeling phenomenon with outward displacement of the external vessel wall that prevents plaque from encroaching into the lumen. The use of angiography alone could also lead to an underestimate of stenosis severity, possibly deferring a clinically indicated revascularization procedure, or could lead to an overestimate of stenosis severity, possibly leading to unnecessary stenting procedures.

## **Index Diagnostic Techniques**

A description of intravascular diagnostic-manufacturers and regulatory status is provided in Appendix D.

## **Intravascular Physiologic Testing Techniques**

### **Coronary Flow Reserve**

CFR utilizes invasive physiologic testing to assess the functional significance of a coronary stenosis. Measurements of CFR are obtained utilizing a Doppler-sensor-tipped intravascular wire to determine the ratio of hyperemia to basal mean flow velocity just distal to the coronary stenosis in question. This ratio is obtained from flow measurements before and immediately after the administration of a vasodilator, such as adenosine. The CFR decreases with increased lesion severity. A CFR  $<2.0$  is typically used as a threshold to determine if an intermediate coronary lesion is physiologically significant (Table 1); however, CFR measurements have not been standardized for guiding stent placement during PCI.

The major limitation in assessing a coronary stenosis with CFR is the influence of microvascular impairment on CFR values. When microvascular circulation is compromised by ventricular hypertrophy or diabetes mellitus, then the CFR may be less than 2.0 (abnormal). An abnormal CFR does not differentiate whether an abnormality exists in the epicardial coronary artery or in the microcirculation. To overcome this limitation, the measurement of an adjacent “normal” coronary vessel has been proposed to provide values for a relative CFR. However, this requires interrogation of an additional vessel, which extends the procedural time and may result in additional complications. Because of these limitations, CFR has not gained wide-spread acceptance.

### **Fractional Flow Reserve**

Coronary pressure wire-derived FFR is defined as the ratio of maximal blood flow achievable in a stenotic coronary artery relative to the maximal flow in the same vessel if it were normal. This index represents the fraction of the normal maximal myocardial flow that can be achieved despite coronary stenosis. Flow measurements are obtained readily by advancing a pressure sensor-tipped coronary angioplasty guide wire across a stenosis and recording the distal pressure at rest and at maximal hyperemia induced with intracoronary or intravenous infusion of the vasodilator adenosine. The ratio between the mean distal pressure at maximal hyperemia and the mean aortic pressure is the FFR. Unlike CFR, FFR is independent of changes in heart rate, blood pressure, or prior infarction, and takes into account the contribution of collateral blood flow. The normal FFR for all vessels under all hemodynamic conditions is 1.0, regardless of the status of microcirculation. An FFR value  $>0.80$  generally excludes ischemia related to a specific

stenosis.<sup>8</sup> The presence of conditions that limit achievement of maximal hyperemia, such as small vessel, diffuse disease, infarcted myocardium, or left ventricular hypertrophy, diminish the reliability of FFR.

FFR can also accurately determine the hemodynamic significance of serial coronary lesions when performed via a slow “pull back method” during continuous intravenous infusion of adenosine, with avoidance of unnecessary procedures that may not provide additional hemodynamic benefit. The long-term followup of the DEFER trial evaluated the appropriateness of stenting a functionally nonsignificant stenosis, and demonstrated that stenting nonsignificant lesions does not improve patient outcome.<sup>13</sup> Five-year outcome after deferral of PCI based on an  $FFR \geq 0.75$  indicated a low risk of cardiac death or myocardial infarction related to such a stenosis of approximately 1 percent per year (a rate not decreased by stenting). Once a PCI is performed, adequacy of the PCI result can be assessed by FFR with established criterion for a successful stent placement an FFR value of  $>0.94$  (Table 1).

Clinical adoption of FFR varies widely, influenced by geographic factors, physician preferences, provider settings (hospital-employed vs. private practice interventionists) and insurance coverage. FFR is currently covered by the Centers for Medicare and Medicaid (CMS) for reimbursement.

**Table 1. Catheter-based anatomic and physiologic criteria associated with clinical outcomes**

Application	IVUS	CFR	FFR
Ischemia detection	$<3-4 \text{ mm}^2$	$<2$	$<0.8$
Deferred angioplasty	NA	$>2$	$>0.8$
Endpoint of stenting	$>9 \text{ mm}^2$ ; $>80\%$ reference area; full apposition (depending on vessel size and volume plus morphology of plaque and target vessel segment)		$>0.94$ (depending on diffuse disease in persistent segment)

CFR = coronary flow reserve; FFR = fractional flow reserve; IVUS = intravascular ultrasound; NA = not applicable

## Intravascular Imaging Techniques

### Intravascular Ultrasound

IVUS is a catheter-based technique that provides tomographic images perpendicular to the length of the coronary arteries. During PCI, IVUS provides high-resolution images of the vessel and lumen geometry, and enables analysis of plaque composition and distribution, as well as guidance of coronary artery stent implantation. IVUS can also be used to quantitatively assess revascularization success or diagnose stent-related complications.<sup>15</sup> However, it does not directly measure the hemodynamic effects of a stenosis. Limitations of the technique include the inability to discriminate between fibrous and lipid-rich plaques and the fact that thrombus formation cannot be easily detected. Modifications of IVUS using analysis of integrated backscatter and the radiofrequency envelope have been reported to improve resolution and sensitivity for the detection of lipid-rich plaques. IVUS elastography that combines ultrasound images with radiofrequency measurements may be able to better detect regions of increased strain prone to rupture. In an effort to improve plaque characterization, IVUS-virtual histology was developed, which combined frequency and amplitude analysis and used an algorithm developed from known tissue types to detect plaques with vulnerability features.

IVUS has been used to guide and optimize stent implantation. It allows the operator to visualize how well the stent is deployed, quantify the residual luminal diameter, and detect complications of stent implantation that require immediate management, such as stent-edge



dissections. IVUS offers optimal stent deployment with only minimal residual luminal stenosis. Attainment of a large luminal diameter minimizes the risk of both stent thrombosis and restenosis. IVUS may have potential value for the stenting of long lesions, bifurcation, ostial and undilatable lesions and for saphenous vein grafts. IVUS is currently covered by CMS for reimbursement.

## **Optical Coherence Tomography**

OCT measures the echo time delay and intensity of backscattered light due to internal microstructure in the tissue in order to create high-resolution (10  $\mu\text{m}$ ) cross-sectional images. Because of the short wavelength of OCT, it will reflect (and detect) very small objects, including blood cells. Therefore, in order for OCT to image the vessel wall, it requires a blood-free field. The original time-domain OCT technique requires continuous flushing with proximal balloon occlusion to displace the blood. Recently, faster data and image acquisition with optical frequency domain imaging has enabled rapid (i.e., 15 to 30 mm/s) imaging with only a 3 to 5 second contrast or saline injection through the guiding catheter (without the need for proximal balloon occlusion). The proposed advantages of OCT are that it provides a clearer picture of plaque structures than IVUS. The potential disadvantage of OCT is limited tissue penetration and, therefore, its inability to consistently image the adventitia and assess plaque burden. The diagnostic information provided by OCT pertains to the very detailed anatomic imaging of plaques, thus making the technique potentially useful for the detection and treatment plaques that are at risk of rupture and also for the assessment of stent apposition. No potential role of OCT in helping to make treatment decisions for intermediate lesions has been described. Recent data suggest that OCT imaging can be performed with similar safety profile as IVUS. The United States Food and Drug Administration (FDA) has recently cleared an OCT device (LightLab Imaging, Inc., Westford, MA) for high resolution vessel and lumen morphology, but CMS does not currently reimburse OCT imaging.

## **Angioscopy**

Intracoronary angioscopy facilitates direct visualization of the plaque surface, color of the luminal surface, presence of thrombus, and macroscopic features of the arterial wall. Angioscopy can assess plaque color and detect red and white thrombus and surface characteristics, such as ulcerations, fissures and flaps. Angioscopy visualizes the luminal surface but is insensitive to subtle differences in plaque. Therefore, the major role of angioscopy is limited to the assessment of the lumen structure before and after interventions. However, angioscopy is rarely used in clinical practice, because it requires a blood-free field of view. The technique, nevertheless, remains valuable for research purposes, with most use occurring in Japan. This imaging modality is not currently covered by CMS.

## **Near Infrared Spectroscopy**

NIRS employs a catheter containing an optic fiber that is used to measure diffuse reflectance signals with near infrared light as an energy source. NIRS yields information about the plaque chemical composition via the pattern of absorption of the light in relation to the wavelength. This pattern is unique for lipid and each of the other plaque elements. A NIRS device (Lipiscan) has been recently cleared by the FDA for the detection of lipid-rich plaque. The clinical premise of NIRS is that lipid-rich plaques could be detected before performing PCI and thus therapeutic decisions could be tailored to the chemical composition of the plaque (e.g., use of embolic

protection devices, selection of stent type). The major limitation of NIRS is that it provides compositional but not structural information. This imaging modality is not currently covered by CMS.

## **Thermography**

Thermography is a catheter-based technique to detect heat released by activated inflammatory cells of atherosclerotic plaques. Temperature differences correlate positively with cell (macrophage) density, which may predict plaque disruption and thrombosis. However, there is no clear evidence that temperature differentials correlate with specific plaques that are at risk of rupture, and without the structural definition obtained from high-resolution imaging techniques, the role of thermography is limited. This imaging modality is not currently covered by CMS.

## **Intravascular Magnetic Resonance Imaging**

Plaque characterization by IMRI may be useful in the detection of plaques with necrotic core and intraplaque hemorrhage. In this technique, an intravascular coil is inserted into the artery or the adjacent vein. IMRI yields adequate resolution to discriminate plaque components, including lipid, collagen, thrombus, and calcium on the basis of biochemical properties. Technical limitations exist in the IMRI coil designs, however, requiring multiple catheter manipulations and repeated imaging. Image quality is also reduced significantly as the intravascular coil moves off axis from the external magnet field. This imaging modality is not currently covered by CMS.

## **Scope of the Review**

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

## **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?

## Methods

The Tufts Evidence-based Practice Center (EPC) reviewed the existing body of evidence on the comparative effectiveness of intravascular diagnostic techniques versus angiography alone in therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes in the management of patients with coronary artery disease (CAD) who are undergoing coronary artery stenting. This report is based on a systematic review of the published scientific literature using established methodologies as outlined in the Agency for Healthcare Research and Quality's (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."<sup>16</sup>

### AHRQ Task Order Officer

The AHRQ Task Order Officer (TOO) assigned to this project was responsible for overseeing all aspects of this report. The TOO facilitated a common understanding among all parties involved in the project, resolved ambiguities, and fielded all EPC queries regarding the scope and processes of the project. The TOO and other staff at AHRQ reviewed the report for consistency, clarity, and to ensure that it conforms to AHRQ standards. Input from the TOO and other staff at AHRQ was incorporated during preparation of the draft and final report.

### External Expert Input

During topic refinement, the initial questions that had previously been nominated for this report were refined with input from a panel of Key Informants who included experts in interventional cardiology, interventional radiology, and noninterventional cardiology; representatives from relevant specialty societies; payers; and a patient representative. After a public review of the proposed Key Questions, the clinical experts were reconvened to form the Technical Expert Panel (TEP), which served in an advisory capacity to help translating the Key Questions into a research protocol, identify important issues, and define parameters for the review of evidence. Discussions among the EPC, TOO, and Key Informants (and subsequently, the TEP) occurred during a series of teleconferences and via email.

### Key Questions

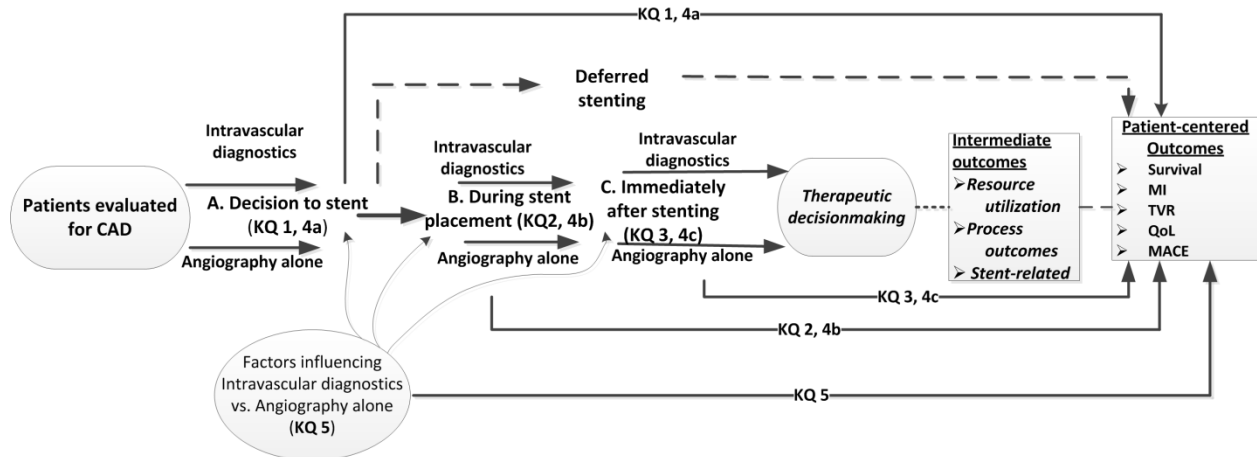
Five Key Questions were posed. Four pertained to outcomes in patients with CAD on the use of intravascular diagnostic applications when compared with angiography (Key Questions 1–3), or different intravascular diagnostic techniques (Key Questions 4), and one (Key Question 5) addressed associations between factors (e.g., patient/physician characteristics, availability of prior noninvasive testing, type of PCI performed) that could influence the effect of intravascular diagnostic techniques compared with angiography (or among different intravascular diagnostic techniques) on outcomes. The exact wording of the Key Questions has been described in the Introduction.

### Analytic Framework

We developed an analytic framework (Figure 1) that maps the Key Questions within the context of the populations of interest, the interventions, comparator, and the outcomes of interest, and the chain of logic that evidence must support to link the interventions to improved health outcomes. The figure illustrates how intravascular diagnostic techniques— compared with

angiography alone—may aid in decisions to stent coronary lesions (A in Figure 1), allow optimization of stent placement during PCI (B in Figure 1), and assessment of immediate results in patients after stent deployment to decide the need for additional procedures (C in Figure 1), and improve short-term (in hospital or discharge to 30 days), medium-term (>30 days to 1 year), and long-term (>1 year) outcomes. Angiography alone is the comparator for Key Questions 1–3. For Key Question 4, the comparator is a different intravascular diagnostic technique from the index intravascular diagnostic technique of interest (head-to-head comparisons of intravascular diagnostic techniques). For Key Question 5, the modifiers of treatment effect included patient/physician characteristics, availability of prior noninvasive testing, and the type of PCI performed.

**Figure 1. Analytic framework**



CAD = coronary artery disease; KQ = Key Question; MACE = major adverse cardiac events; MI = myocardial infarction; QoL = quality of life; TVR = target vessel revascularization

## Literature Search

We conducted literature searches for studies in MEDLINE<sup>®</sup> (from inception to August 31, 2012) and the Cochrane Central Trials Registry<sup>®</sup> (through the second quarter of 2012) without any language restriction. All studies conducted in adult human subjects were screened to identify articles relevant to each Key Question. Our search included terms for intravascular diagnostic techniques, myocardial ischemia, revascularization, stents, and relevant research designs (see Appendix A for complete search strings). We also reviewed the reference lists from recently published systematic reviews on intravascular diagnostic techniques for potentially eligible studies. We excluded narrative reviews, editorials, and letters to the editor.

With input from the TEP, we compiled a list of professional organization meetings that published oral presentations and poster abstracts on intravascular diagnostic techniques addressing our Key Questions. We retrieved and screened relevant abstracts from professional and summit conference meetings that were available online through the following resources: Transcatheter Cardiovascular Therapeutics ([www.tctmd.com](http://www.tctmd.com)) indexed until June 2012, the American Heart Association ([www.aha.org](http://www.aha.org)) indexed from 2009 through June 2012, and the American College of Cardiology ([www.cardiosource.com](http://www.cardiosource.com)) indexed from 2009 through June 2012. We also searched the ClinicalTrials.gov Web site to identify ongoing trials.

## **Study Selection and Eligibility Criteria**

We screened titles and abstracts of citations identified from our literature search using the predefined eligibility criteria. The titles and abstracts were initially screened by one investigator; rejected abstracts were rescreened by a second investigator. Abstracts equivocal for inclusion would trigger an automatic full-text review. Full-text articles of abstracts that met screening criteria were retrieved and examined by two investigators to confirm their eligibility. All disagreements were resolved in consultation with a senior investigator. Full-text articles published in non-English languages were translated using Google™ Translate (translate.google.com). We focused only on direct comparative studies for this review. We excluded studies of indirect comparisons or that lacked a distinct comparator group. We did not include studies that solely compared stenting versus medical therapy. We also excluded studies that compared different thresholds within a single intravascular diagnostic technique. Eligibility criteria for inclusion were as follows.

## **Populations and Conditions of Interest**

We included studies conducted in adults ( $\geq 18$  years) with CAD who were undergoing coronary artery stenting. We included the following conditions of interest, if reported in individual studies: CAD due to intermediate coronary stenoses (40% to 70%), either ischemic or nonischemic; left main artery lesions; any type of complex coronary lesions (e.g., long diffuse lesions, tandem lesions, bypass conduit vessel lesions, bifurcation lesions, total occlusions, ostial lesions, stent thromboses, thrombotic and nonthrombotic lesions); types of acute coronary syndrome (ST segment elevation myocardial infarction [STEMI] and non-STEMI); unstable and stable angina; in-stent restenosis; and stent fractures.

Additional subgroups of interest for all Key Questions included: patients with and without diabetes; patients with chronic inflammation (e.g., systemic lupus erythematosus); patients with atherosclerosis following heart transplantation.

## **Interventions**

For all Key Questions, we included intravascular diagnostic techniques that evaluate morphological or physiological parameters of coronary lesions and are presently employed in clinical care. The most commonly employed intravascular diagnostic techniques included FFR and IVUS. If available, also included were interventions that are primarily investigational at present, such as IVUS-virtual histology, OCT, elastography, NIRS, thermography, angioscopy, and IMRI), 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.

## **Comparators**

Coronary angiography 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.

We did not include studies that solely compared stenting versus medical therapy. We also excluded studies that compared different thresholds within a single intravascular diagnostic technique.

## Outcomes

The outcomes of interest were categorized as therapeutic decisionmaking, intermediate outcomes, or patient-centered outcomes. Outcomes were measured at three time points: short-term (up to 30 days after the procedure), medium-term (>30 days to 1 year), and long-term (>1 year).

### Therapeutic Decisionmaking

- **Key Question 1:** In patients with CAD, the 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, the change in the type of stent or number of stents or length of stent after the application of intravascular diagnostic
- **Key Question 3:** Immediately after PCI, the change in the decision about the need for additional interventions or modifications to stent placement

### Intermediate Outcomes

- Process outcomes (technical success rates assessed by QCA, such as proportion of successful completion of attempted procedures or proportion of interpretable results in completed procedures, total procedural time required, fluoroscopy time, and volume of contrast medium used)
- Periprocedural complications (e.g., vessel dissection, bleeding, repeat PCI, or emergency coronary bypass surgery)
- Resource utilization (e.g., number of guide catheters, wires, balloons, and stents)
- Stent-related complications (e.g., restenosis, acute stent thrombosis, and dissection)
- Other measures (e.g., cardiac imaging findings [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, MI, repeat revascularizations or composites of major adverse cardiac events [MACE], freedom from angina, quality of life, and quality-adjusted survival)

## Sample Size and Timing

We did not specify a minimum sample-size threshold. We included studies of any duration of followup.

## Eligible Study Designs

We included all comparative studies, including randomized controlled trials (RCTs) and nonrandomized comparative studies that provide data directly comparing intravascular diagnostic technique and angiography with angiography alone or one intravascular diagnostic technique with another. We excluded narrative reviews and case reports.

## Settings

Application of intravascular diagnostic techniques and use in the following settings were considered: tertiary care centers or community hospitals; in-hospital or stand-alone catheterization laboratories; and emergency or nonemergency catheterizations.

## Data Extraction

Each study extraction was conducted by one investigator and reviewed by at least one other. Any disagreements were resolved by discussion in team meetings. Data were extracted into standard forms in Microsoft® Word. The basic elements included fields that addressed population characteristics, sample size, study design, analytic details, and outcomes.

We extracted data including basic demographics (such as age, sex, race); comorbidities (such as diabetes, hypertension); clinical characteristics (such as percent ejection fraction, location of stenosis, lesion type); and modifying factors associated with the application of intravascular diagnostic and outcomes. We tested the extraction form on several studies and revised the form as necessary before commencing full data extraction of all articles.

## Data Synthesis

To evaluate the effect of an intervention on outcomes, we performed DerSimonian and Laird random effects model meta-analyses of the risk ratio of binary data or mean differences of continuous outcomes between interventions where studies had sufficiently similar population and had the same comparison of interventions and the same outcomes. For each specific outcome of interest, we performed separate meta-analyses at specific time points (i.e., in-hospital,  $\leq 1$  year, and  $>1$  year), chosen based on available relevant data. We sought input from the clinical expert (cardiologist) on our team to assess whether studies were too clinically heterogeneous for meta-analysis to be appropriate. For example, if target vessel revascularization was not reported, we used target lesion revascularization.

When possible, we preferentially evaluated the net change of continuous outcomes (the difference between the intervention of interest and the control intervention in the 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/or final values. For outcomes that were reported as final measurements, 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 to have high risk of bias (see assessment of risk of bias) to see if these studies impacted inferences drawn from syntheses of studies with low and medium risk of biases only.

The findings of the report were presented according to the order of the Key Questions. Within each Key Question, findings were presented separately for therapeutic decisionmaking, intermediate, and patient-centered outcomes. They were further categorized by specific time periods: short term (in hospital, discharge to 30 days), medium-term ( $>30$  days to 1 year), and long-term ( $>1$  year). Outcome data were presented in evidence tables and were summarized in the full text and the Executive Summary of the report. All included studies were summarized in narrative form and in summary tables, which tabulated the important features of the study



populations, design, intervention, outcomes, and results. We did not conduct statistical analyses to assess publication bias, as most of the statistical methods for detecting or correcting for publication bias have specific drawbacks. We attempted to mitigate the issue by searching grey literature sources available online (through June 2012) from [www.tctmd.com](http://www.tctmd.com), [www.aha.org](http://www.aha.org), and [www.CardioSource.org](http://www.CardioSource.org).

## **Summary Tables**

Summary tables succinctly report measures of the main outcomes evaluated. We included information regarding study design, intravascular diagnostic technique, country, age data, gender data, sample size, study duration, patients' medical characteristics, and study quality. For continuous outcomes, we included the mean outcome values, their 95% confidence intervals (CI), standard deviations (SD) or other measures of variability, and when available, the mean difference (between groups) and its corresponding P value or CI, as appropriate. For categorical (dichotomous) outcomes, we reported the number of events and total number of patients for each intervention and relative risk metrics (odds ratios, risk ratios or hazard ratios) with their corresponding 95% CI and associated P value. We created separate summary tables based on the type of interventions and the type of outcomes.

## **Risk of Bias (Overall Methodological Quality) of Individual Studies**

We assessed the risk of biases (methodological quality) for each individual study using the assessment instrument detailed by the Agency for Healthcare Research and Quality in its "Methods Guide for Effectiveness and Comparative Effectiveness Reviews," hereafter referred to as "the Methods Guide."<sup>16</sup> Briefly, we rated each study as being of 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 graded the strength of the body of evidence for each analysis within the Key Questions as per the Methods Guide<sup>16</sup> and an updated methods paper,<sup>17</sup> with modifications as described below. The appraisal of the strength of evidence relied on studies rated as being at a low-or medium risk of bias. 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, 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 we broadly define here as any outcomes that affect the patient's well-being.

We rated the strength of evidence with one of the following four strengths (as per the Methods Guide): High, Moderate, Low, and Insufficient. Ratings were assigned based on our level of confidence that the evidence reflected the true effect for the major comparisons of interest. 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.

These ratings provide a shorthand description of the strength of evidence supporting the major questions we addressed. However, by necessity they may oversimplify the many complex issues involved in the appraisal of a body of evidence. It is important to remember that the 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.

## Assessing Applicability

We assessed applicability of studies using the individual study eligibility criteria and baseline characteristics of the included population. Characteristics that could affect applicability to a wide population included narrow study eligibility criteria (e.g., narrow range of demographics) and dated studies using practices that are no longer applicable to contemporary practices. We also summarized how well the evidence applies to clinical practice. We provided an overall summary table describing key conclusions about applicability of bodies of evidence, and also provided comments on specific issues that affected applicability.

## Protocol Registration

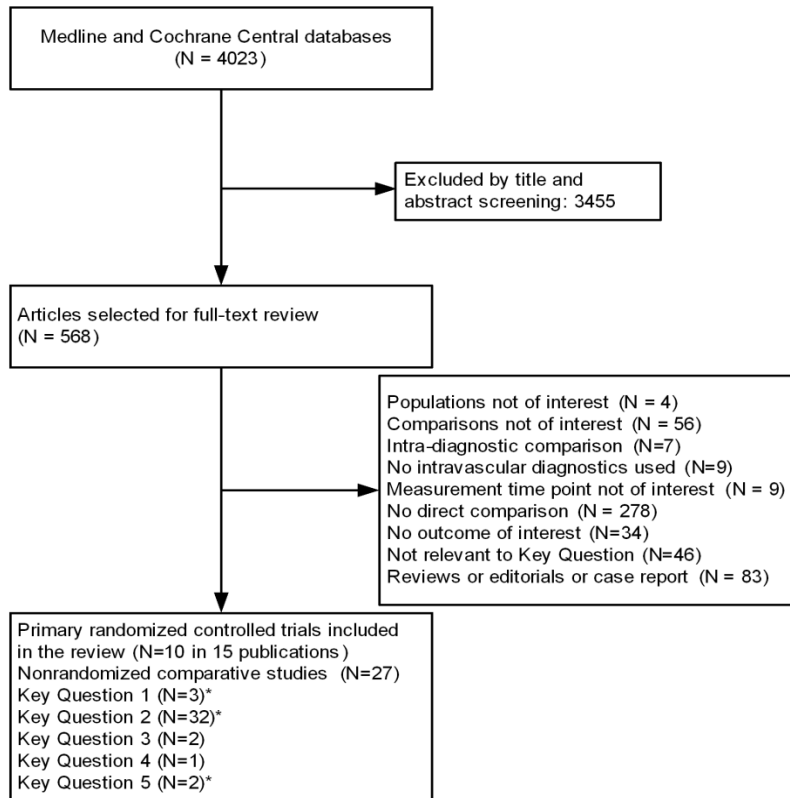
A Comparative Effectiveness Review protocol was submitted and published on the AHRQ Effective Health Care Program Web site on August 29, 2011 ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)). Some minor amendments to the posted protocol were made at the time of preparation of this draft. These included a slight rewording of the Key Questions (e.g., PCI replaced by stenting), and a restructuring of the outcome categories (short-, intermediate-, and long-term outcomes were changed to therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes).

# Results

The literature search yielded 4,023 citations. From these, 568 articles were provisionally accepted for review on the basis of the abstracts and titles (Figure 2). After screening their full texts, 37 studies, published in 42 articles, were judged to have met the inclusion criteria. The grey literature search yielded no additional 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 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); within diagnostic technique comparisons (e.g., comparison between different criteria of the same diagnostic technique; 7 articles); irrelevant or incomplete measurement time points (e.g., comparison between intravascular diagnostic techniques and angiography only at followup; 9 articles); and no population of interest (4 articles). See Appendix B for a list of the excluded studies with the reason for exclusion.

The 37 accepted, nonoverlapping studies (in 42 articles) had data addressing at least one of the five Key Questions are available for IVUS and FFR, and no comparative studies are available for the remaining investigational intravascular diagnostic techniques. Summary Tables with the descriptions of each study are in Appendix C.

**Figure 2. Literature flow diagram**



N = number

\* Indicates some overlapping studies across 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 Points**

- There is a moderate strength of evidence favoring the adjunctive use of FFR during angiography in deciding to stent an intermediate coronary lesion (50% to 70% stenosis), using an FFR threshold  $<0.80$ ; the use of FFR confers a lower risk of the composite endpoint of death or MI, or of MACE; and leads to fewer stents implanted and reduces the costs of the procedure.
- The evidence supporting the adjunctive use of FFR during angiography in deciding to stent an intermediate coronary lesion was derived from studies that focused on men with intermediate coronary disease and lower grade angina, and excluded patients with left main disease.
- There is insufficient evidence regarding the use of any techniques other than FFR, as none of the studies reviewed techniques other than FFR to decide whether a coronary lesion required stenting.

## **Summary of Evidence**

Our appraisal of the strength of evidence relied on studies rated as being at a low- or medium risk of bias. 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 ( $\geq 50\%$  to 70% stenosis), using an FFR threshold  $<0.80$ . The use of FFR in these lesions to decide whether to stent led to fewer stents being implanted, reduced the cost of the procedure, and conferred a lower risk of the composite endpoint of death or MI, or of major adverse cardiac events (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 adjunctive 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 (up to 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 and MI or MACE) in the medium term ( $>30$  days to 1 year) and long term ( $>1$  year). None of the studies reported patient-centered outcomes at 30 days after the procedure.

With respect to Key Question 1, there is insufficient evidence regarding the use of any intravascular diagnostic technique aside from FFR, as none of the studies reviewed other techniques.

## Available Evidence

We identified three studies, including one RCT (Fractional Flow Reserve versus Angiography for Multivessel Evaluation [FAME] trial in three publications) and two nonrandomized studies evaluating the use of FFR to decide whether a coronary lesion needs intervention, as compared with angiography. No eligible studies on other intravascular diagnostic techniques were found to address this Key Question. Three studies in five publications compared the use of FFR-guided stenting with stenting guided by angiography alone.<sup>18-22</sup> Two related RCTs—DEFER<sup>13</sup> and FAME II<sup>12</sup>—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 the trial compared FFR-guided stenting plus optimal medical therapy with optimal medical therapy alone.

One RCT (with three publications), the FAME trial, followed 1,005 adult patients with at least a  $\geq 50$  percent diameter stenosis in two or more major epicardial vessels, over 2 years.<sup>18,20,21</sup> Also included were patients with a recent nonST-segment elevation MI for less than 5 days if their peak creatine kinase (CK)-MB was  $< 1,000$  IU or if they had undergone PCI in the past. Excluded were patients with left main coronary artery disease, previous CABG, or a recent ST-segment elevation MI within 5 days. The average age of these patients was 64 years, and the proportion of included men was 74 percent. The proportion of patients with diabetes was 25 percent, hypertension 67 percent, and dyslipidemia 73 percent. The majority of patients had Canadian Cardiovascular Society angina grade I to III; less than 20 percent of the included patients had grade IV angina. After randomization, lesions in the FFR-guided PCI group had drug-eluting stent implantation only if the FFR was 0.80 or less in epicardial vessels that demonstrated a  $\geq 50$  percent diameter stenosis by angiogram. In the angiography-guided PCI group, all lesions underwent drug-eluting stent implantation. The choice of stent implantation was at the discretion of the surgeon. The FAME trial was rated as being at a low risk of bias.

Two nonrandomized studies compared the use of FFR-guided stenting with stenting guided by angiography alone.<sup>19,22</sup> One followed 137 patients prospectively for more than 2 years.<sup>22</sup> In this study, patients who had stable angina with stenoses in two or more coronary arteries were included; excluded patients were those who had undergone a previous CABG, experienced a recent acute MI, or those with an ejection fraction  $< 50$  percent. The average age of included patients was 62 years; 77 percent were men. The proportion of patients with diabetes was 38 percent, hypertension 74 percent, and dyslipidemia 63 percent. The study lacked data on other baseline characteristics. The study was rated as being at a medium risk of bias due to the lack of adjusted analyses.

The second nonrandomized study followed 154 consecutive first-time acute MI patients with totally occluded lesions (142 of the 155 total stenotic lesions).<sup>19</sup> Patients in the intervention group were prospectively followed for 2 years; however, the comparison group was a historical cohort from the same single-center. The average age of included patients was 63 years; 76 percent were men. The proportion of patients with diabetes was 16 percent and dyslipidemia 23 percent. The proportion of patients with left-anterior descending culprit stenoses was significantly higher in the FFR-guided stenting compared with stenting guided by angiography alone. The proportion of patients with hypertension was not documented, and the study lacked data on other baseline characteristics. The study was rated as being at a high risk of bias due to comparisons to a historical control and the lack of adjusted analyses.

## Therapeutic Decisionmaking

Overall, the adjunctive use of FFR during angiography aids in deciding whether to stent an intermediate coronary lesion ( $\geq 50\%$  stenosis), using an FFR threshold  $< 0.80$ . All three studies included for Key Question 1<sup>18-22</sup> reported data for therapeutic decisionmaking outcomes comparing FFR-guided stenting with stenting guided by angiography alone.

The therapeutic decisions whether or not to stent were made on the basis of FFR threshold; though the threshold used varied considerably across the three studies. Among patient referred for revascularization, stent implantation was conducted in 874 of the 1,387 lesions (63%) with an FFR  $\leq 0.80$  in the FAME trial. No stents were placed in the remaining 513 (37%) lesions with FFR  $> 0.80$  in patients with stable multivessel coronary disease.<sup>21</sup> In the prospective nonrandomized comparative study, PCI was deferred in 75 of the total 128 vessels (58% with an average FFR of 0.86) and the remaining 53 vessels with an average FFR of 0.67 underwent PCI and stenting in patients with stable multivessel coronary disease.<sup>22</sup> In the prospective nonrandomized comparative study with a historical comparator, stent implantation in patients with acute MI was performed in 40 lesions (FFR  $< 0.94$ ); the remaining 37 lesions (FFR  $\geq 0.94$ ) underwent direct angioplasty without stenting.<sup>19</sup>

## Intermediate Outcomes

### Resource Utilization

Overall, the use of FFR reduces resource utilization in the short term (up to 30 days after the procedure), as compared with angiography alone. In the FAME trial, the number of hospital days at baseline admission was significantly lower in the FFR-guided group, as compared with the group who received stenting guided by angiography alone (3.4 vs. 3.7 days;  $p=0.05$ ).<sup>21</sup> The remaining two nonrandomized comparative studies did not report this outcome.<sup>19,22</sup>

None of the included studies reported data on medication use during the procedural time period. The number of stents implanted per patient was significantly lower in the FFR-guided group, as compared with the group receiving stenting guided by angiography alone, in both the FAME trial<sup>21</sup> and in one prospective nonrandomized comparative study.<sup>22</sup> The number of stents implanted per patient was 1.9 versus 2.7 in the FAME trial,<sup>21</sup> and 1.04 versus 1.28 in the prospective nonrandomized study.<sup>22</sup> The second prospective nonrandomized study (with a historical control) did not report this outcome.<sup>19</sup>

The cost of procedure was reported in all three studies.<sup>19,21,22</sup> The cost of the procedure, including materials used during PCI, was significantly lower in the FFR-guided group, as compared with the group who received stenting guided by angiography alone, in all three studies. Both the FAME trial and one prospective nonrandomized study reported cost individually per material used during PCI.<sup>18,22</sup> In the FAME trial, individual cost per material was lower with FFR-guided stenting than in with angiography-guided stenting, although no formal statistical comparisons of individual cost per material were reported between groups. In the prospective study, the cost of the guidewires was significantly higher in the FFR-guided stenting group; however, this was off-set by the increased use and cost of balloons and stents in the group whose stents were guided by angiography alone.<sup>22</sup>

There were no significant differences in procedure time between the groups, based on the findings of the FAME trial<sup>21</sup> and one prospective nonrandomized comparative study.<sup>22</sup> In the FAME trial, contrast use was significantly lower in the FFR-guided stenting than in the angiography-guided stenting (272 vs. 302 mL;  $p<0.001$ ). However, no significant difference in

the use of contrast was observed between the two groups in the nonrandomized comparative study. Radiation exposure time was similar between the two groups in this study.

### **QCA Process Outcomes**

Two nonrandomized comparative studies, reported data for in-hospital process outcomes comparing FFR-guided stenting with stenting guided by angiography alone.<sup>19,22</sup>

The net changes in the minimal lumen diameter measurements of the FFR and angiography alone groups, from baseline to postprocedure, reported in two prospective nonrandomized comparative studies, was inconsistent.<sup>19,22</sup> One was rated as being at a medium risk of bias, and reported no significant difference between the two groups (MLD net difference 0.02 mm; not significant (NS) and diameter stenosis net difference 1%; NS).<sup>22</sup> The second, with a historical control and rated as being at a high risk of bias, reported an unfavorable effect for FFR-guided stenting over stenting guided by angiography alone (MLD net difference -0.3 mm;  $p < 0.001$  and diameter stenosis net difference 9.0%;  $p < 0.001$ ).<sup>19</sup>

The net changes in percent diameter stenosis measurements between the FFR-guided group and the group who received stenting guided by angiography alone, from baseline to postprocedure (reported in two prospective nonrandomized studies), were inconsistent.<sup>19,22</sup> One (rated as being at a medium risk of bias) reported no significant difference in percent diameter stenosis between the groups. The second (with a historical control; rated as being at a high risk of bias) reported a favorable effect for FFR-guided stenting over stenting guided by angiography alone (percent diameter stenosis net difference -0.3;  $p < 0.001$ ).<sup>19</sup>

### **Stent-Related Outcomes**

One prospective nonrandomized comparative study with a historical control reported nonsignificantly higher rates of reocclusion and restenosis with FFR-guided stenting, as compared with stenting guided by angiography alone.<sup>19</sup> None of the included studies reported data on acute stent thrombosis.

### **Patient-Centered Outcomes**

There was no incidence of in-hospital complications of CABG or death reported in any of the three included studies.<sup>19,21,22</sup> Only one prospective study (nonrandomized) reported data on repeat target lesion revascularization during in-hospital stay, and found no statistically significant difference between groups.<sup>22</sup>

The FAME trial reported periprocedural infarctions diagnosed on the basis of increases in CK-MB (three to five times the upper limit of normal) as 2.4 percent in the FFR-guided stenting versus 3.2 percent angiography-guided stenting.<sup>20</sup> The FAME trial reported the absolute mean difference of MACE at discharge as -2.2 percent between the two groups (no statistical significance was provided).<sup>20</sup> One of the nonrandomized comparative studies, reported a nonsignificantly lower proportion of in-hospital non-Q wave MI and cumulative MACE with FFR-guided stenting, as compared with stenting guided by angiography alone.<sup>22</sup> The prospective nonrandomized comparative study (with a historical comparator) reported no cardiac deaths during in-hospital stay.<sup>19</sup> None of the included studies reported patient-centered outcomes at 30 days after the procedure.

All three studies reported no significant difference between groups for the outcome of death in either the medium or long terms.<sup>19,21,22</sup> There was no significant difference in MI between groups in the FAME trial 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% CI 0.40, 0.95).<sup>21,22</sup> The FFR group also displayed a significant decrease in the composite outcome of death or MI (RR 0.66, 95% CI 0.44, 0.98 at 1 year; RR 0.65, 95% CI 0.45, 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, 1.05 at 1 year; RR 0.84, 95% CI 0.59, 1.18 at 2 years). While the FAME trial significantly favored FFR (RR 0.72, 95% CI 0.54, 0.96) for the primary outcome of MACE—defined as death, MI, and repeat revascularization at 1 year—this did not reach statistical significance at 2 years (RR 0.80, 95% CI 0.62, 1.02).<sup>20,21</sup>

In the prospective nonrandomized study, there was no significant difference in MI between groups at 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 at more than 2 years (8% in FFR vs. 27% in angiography alone;  $p < 0.01$ ).<sup>22</sup> The other prospective nonrandomized comparative study (which employed a historical control), 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 angiography alone group (\$14,315 vs. \$16,700, respectively;  $p < 0.001$ ).

Only the FAME trial examined data on patient-reported outcomes, including the number of patients free from angina, composite endpoint of the number of patients without event and free from angina, and intake of antianginal medications at 1 and 2 year followup.<sup>20,21</sup> The trial also 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 vs. 64.7 in the angiography alone). Although a higher proportion of patients were without an event and were free from angina (73% in the FFR-guided stenting group vs. 68% in the group receiving stenting guided by angiography alone), there was no significant difference between the groups for all patient-reported outcomes.

**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 therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes?**

### **Key Points**

- When using IVUS to guide stent deployment, there is a moderate strength of evidence from nine RCTs and 22 nonrandomized studies that supports a reduction in repeat revascularization and restenosis, but no significant differences in mortality and MI, as compared with angiography alone.
- The evidence supporting adjunctive use of IVUS during angiography to guide stent deployment 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, which limits applicability of the evidence.



- There is insufficient evidence for all techniques other than IVUS (one available study regarding the use of FFR, and no studies for all other techniques) to guide and optimize stent deployment.

## Summary of Evidence

Overall, there is a moderate strength of evidence that supports a significant reduction in repeat revascularization and restenosis, but no significant difference in mortality and 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. With regards to 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, reveals no statistically significant differences in QCA outcomes in the short- and medium-terms, and lowers the risk of stent-related outcome of restenosis in the medium-term, as compared with angiography alone. For patient-centered clinical outcomes, there is a moderate strength of evidence that supports no significant difference in mortality, MI, and MACE, but reveals a significant benefit in decreasing repeat revascularization, when using IVUS to guide bare-metal stent deployment, as compared with angiography alone.

There is insufficient evidence from one nonrandomized study regarding the use of FFR in determining the need for additional therapy (dilation) after stent deployment. There is insufficient evidence for all other techniques to answer Key Question 2, as no comparative studies evaluated techniques other than IVUS and FFR.

## Available Evidence

We identified 32 studies reporting direct comparisons of two intravascular diagnostic techniques, IVUS (31 studies) and FFR (1 study), with angiography alone in optimizing stent deployment.

### IVUS Versus Angiography Alone in Stent Deployment

We identified nine RCTs (in 11 publications)<sup>23-33</sup> and 22 nonrandomized comparative studies<sup>34-55</sup> comparing IVUS-guided stent deployment with stenting guided by angiography alone.

Two RCTs were rated as being at a low risk of bias,<sup>29,32</sup> six at a medium risk of bias,<sup>23,25-27,31,33</sup> and one at a high risk of bias.<sup>28</sup> Among the RCTs, sample sizes ranged from 42 to 800, and the average ages of patients ranged from 55 to 66 years. Followup durations ranged from 6 months to 2.5 years. The proportion of men ranged from 62 to 100 percent. The proportion of patients with diabetes ranged from 7.5 to 100 percent (9 RCTs). The proportion of patients with dyslipidemia ranged from 42 to 94.5 percent (9 RCTs), and those with hypertension ranged from 22 to 69.5 percent (9 RCTs). All but one RCT<sup>27</sup> excluded patients with left main disease or acute MI. All but two RCTs recruited patients before 2000;<sup>26,27</sup> both were conducted in Eastern Europe. One RCT evaluated PCI with long stent implantation.<sup>31</sup>

Among the 22 included nonrandomized comparative studies, eight nonrandomized comparative studies were rated as being at a high risk of bias,<sup>37-40,46,47,49,51</sup> while the rest at a medium risk of bias.<sup>34-36,41,42,44,45,48-50,52-55</sup> Six were conducted prospectively<sup>35,38,41,45,50,55</sup> and

eight retrospectively,<sup>34,36,37,39,42,43,47</sup> seven were registry-based (two single center and five multicenter),<sup>40,44,48,49,52-54</sup> and one was cross-sectional.<sup>51</sup> Sample sizes ranged from 34 to 9,070, and the average ages of patients ranged from 55 to 66 years (19 studies). Followup durations ranged from 30 days to 3 years. The proportion of patients with diabetes ranged from 7.1 to 47.1 percent (22 studies). The proportion of patients with dyslipidemia ranged from 25.5 to 91.2 percent (21 studies<sup>34-49,51-55</sup>). The proportion of patients with hypertension ranged from 19 to 91.2 percent (21 studies<sup>34-49,51-55</sup>). Three of the 22 total nonrandomized comparative studies excluded patients with left main disease or acute MI.<sup>35,47,48</sup> Three evaluated patients with only acute MI;<sup>40,52,55</sup> one compared patients with distal and nondistal left main disease,<sup>47</sup> and two others included patients with only unprotected left main disease.<sup>43,49</sup>

In total, 29 studies reported data for in-hospital outcomes (nine RCTs and 19 nonrandomized comparative).<sup>23,25-29,31-51,53,55</sup> Reported in-hospital outcomes of interest included clinical outcomes, diagnostic and therapeutic decisionmaking, process outcomes, periprocedural complications, and stent-related outcomes. Short-term outcomes (30 day outcome) was reported in eight studies (two RCTs<sup>29,31</sup> and six nonrandomized comparative<sup>40,44,52-55</sup>). Medium-term outcomes (>30 days to 1 year) were reported in 24 studies (seven RCTs<sup>23,24,26,29,31-33</sup> and 17 nonrandomized comparative studies<sup>34-46,52-55</sup>), and long-term outcomes (>1 year) were reported in nine studies (three RCTs<sup>25,27,30</sup> and six nonrandomized comparative studies<sup>47-49,53-55</sup>).

## Therapeutic Decisionmaking

Overall, the use of IVUS during PCI can aid the operator in optimizing stent deployment, as compared with angiography alone. Three RCTs<sup>29,32,33</sup> and three nonrandomized comparative studies<sup>38,43,47</sup> reported data on changes in therapeutic decisionmaking resulting from the use of IVUS in optimizing stent placement. In the RCTs, a significantly higher proportion of patients achieved optimal stent placement on the basis of IVUS guidance;<sup>29</sup> almost one-half of the patients received further therapy for an underexpanded stent and repeat balloon angioplasty;<sup>32</sup> and more than one-third underwent additional dilation due to not reaching the IVUS criterion<sup>33</sup> in the IVUS-guided PCI group as compared with the angiography-guided PCI group.

Three nonrandomized comparative studies reported a significantly higher proportion of patients achieving optimal stent placement on the basis of therapeutic decisionmaking guided by IVUS use, which included additional postdilation, debulking, and angioplasty, or a second stent deployment.<sup>38,43,47</sup>

## Intermediate Outcomes

### Resource Utilization

Meta-analysis of four RCTs<sup>26,27,29,31</sup> revealed a nonstatistically significant increase in the use of glycoprotein IIb/IIIa inhibitor in the IVUS-guided stenting (summary RR 1.27; 95% CI 0.76, 2.12). One nonrandomized study reported a significant increase in the use of glycoprotein IIb/IIIa inhibitor in the IVUS group, as compared with the angiography alone group (16% vs. 2.8%;  $p < 0.001$ ).<sup>55</sup> In contrast, another reported a significant decrease in the use of glycoprotein IIb/IIIa inhibitor in the IVUS group, over angiography alone (9.8% vs. 12.8%;  $p < 0.001$ ).

Across four RCTs<sup>23,25,27,29</sup> and two nonrandomized comparative studies,<sup>36,51</sup> two RCTs<sup>27,29</sup> and one nonrandomized comparative study<sup>51</sup> reported significantly longer procedure time in IVUS, while the two other RCTs<sup>31,33</sup> and a nonrandomized comparative study reported no significant difference between groups.<sup>36</sup>

Three RCTs<sup>23,27,29</sup> and one nonrandomized comparative study<sup>51</sup> reported significantly longer fluoroscopy time in the IVUS group over angiography alone, while the other nonrandomized comparative study reported no significant difference between the two groups.<sup>36</sup>

Two RCTs<sup>27,29</sup> reported a significantly increased volume of contrast medium used in the IVUS group over angiography alone, while the remaining RCT<sup>23</sup> and both nonrandomized comparative studies<sup>36,51</sup> reported no significant difference between groups.

The number of guidewires used was similar in both groups in one RCT<sup>29</sup> and one nonrandomized comparative study.<sup>36</sup> The use of stents was similar in both groups in four RCTs,<sup>23,25,27,29</sup> and seven nonrandomized comparative studies, with two exceptions: more stents per patient were used in the IVUS group, compared with the group who received stents guided by angiography alone, in one RCT<sup>31</sup> and one nonrandomized study.<sup>34</sup> The average number of balloons utilized during procedure was similar between groups in two RCTs<sup>23,25</sup> and one nonrandomized comparative study,<sup>36</sup> while one RCT<sup>29</sup> and two nonrandomized comparative studies<sup>44,55</sup> showed the IVUS-guided group utilizing significantly more balloons compared with the group who received stents guided by angiography alone.

One RCT<sup>24</sup> and two nonrandomized comparative studies<sup>36,51</sup> reported an increase in initial cost in the IVUS group relative to the angiography alone group, owing to the extra procedure time and increased utilization of catheters, balloons, and stents. The hospitalization stay was similar between groups in the one RCT reporting data on hospitalization after procedure.<sup>29</sup> No other studies reported data on this outcome.

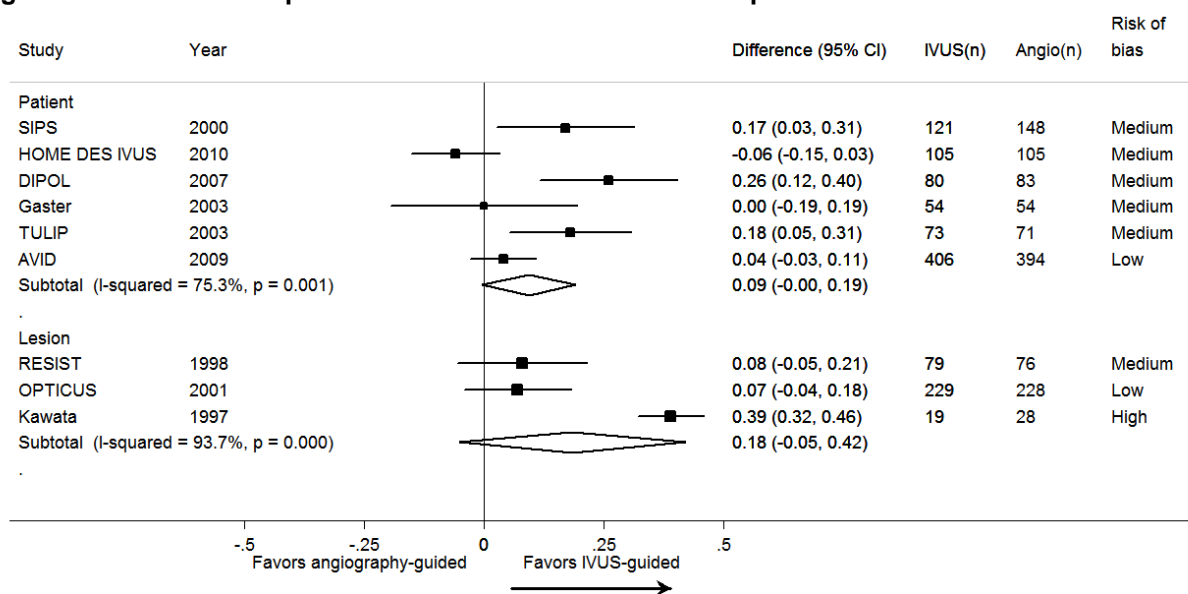
In summary, the IVUS group had a significantly longer procedural time and fluoroscopy time, as compared with angiography alone. There was a nonsignificantly increased utilization of glycoprotein IIb/IIIa inhibitor, contrast medium, or other resources, including guidewires, stents, and balloons during the procedure in the IVUS group over angiography alone. Generally, there were no significant differences between groups for periprocedural complications or stent-related complications.

## **QCA Process Outcomes**

### **In-Hospital MLD**

Some studies reported QCA process outcomes by lesion and some by patients, complicating synthesis because each patient can contribute to multiple lesion-level data points (which are correlated). Treating data on lesions nested within patients as independent observations will underestimate the standard error of the effect size leading to bias. Meta-analyses of the net changes in MLD measurements between IVUS-guided stenting and stent deployment guided by angiography alone, from baseline to postprocedure, conducted across nine RCTs<sup>23,25-29,31-33</sup> (six reporting by patients<sup>23,25-27,31,32</sup> and three reporting by lesions<sup>28,29,56</sup>) revealed consistent small gains favoring IVUS, but no statistically significant difference between groups (Figure 3).

**Figure 3. RCTs of in-hospital minimal lumen diameter: forest plot**

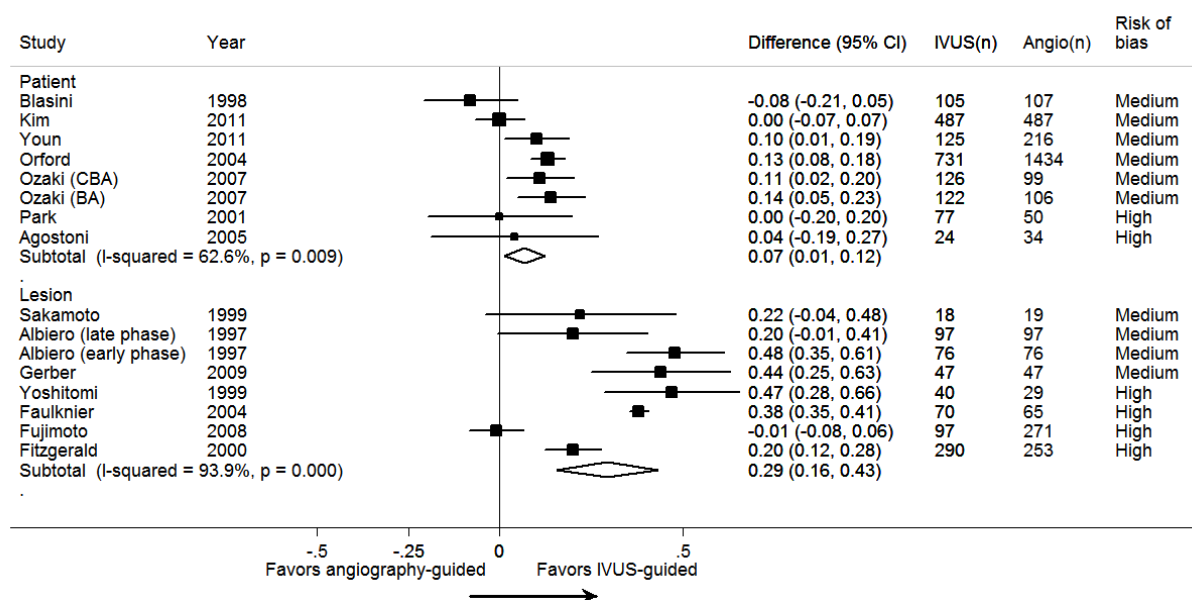


Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n = number  
 Notes: Estimates favoring IVUS are in the direction of the arrow, in contrast to Figures 7-10 on diameter stenosis.  
 A confidence interval that crosses 0 indicates no significant mean difference; values >0 indicate that a larger minimal lumen diameter was achieved in the IVUS group over angiography alone group.

However, meta-analysis of seven nonrandomized comparative studies reporting eight sets of patient-level data,<sup>35,41-43,47,48,55</sup> and seven nonrandomized comparative studies reporting eight sets of lesion-level data,<sup>34,37-39,45,46,50</sup> both revealed a significant difference, indicating a favorable effect for IVUS-guided stenting over stent placement guided by angiography alone (Figure 4), with significant statistical heterogeneity ( $I^2 = 63\%$  for patient-level; 94% for lesion-level analyses). Excluding studies rated as being at a high risk of bias did not change the estimates.

In summary, for in-hospital MLD, the available RCTs and observational data showed conflicting results, and we therefore cannot draw a conclusion as to whether the use of IVUS significantly increases postprocedural MLD.

**Figure 4. Nonrandomized comparative studies of in-hospital minimal lumen diameter: forest plot**



Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n = number

Notes: Estimates favoring IVUS are in the direction of the arrow, in contrast to Figures 7-10 on diameter stenosis.

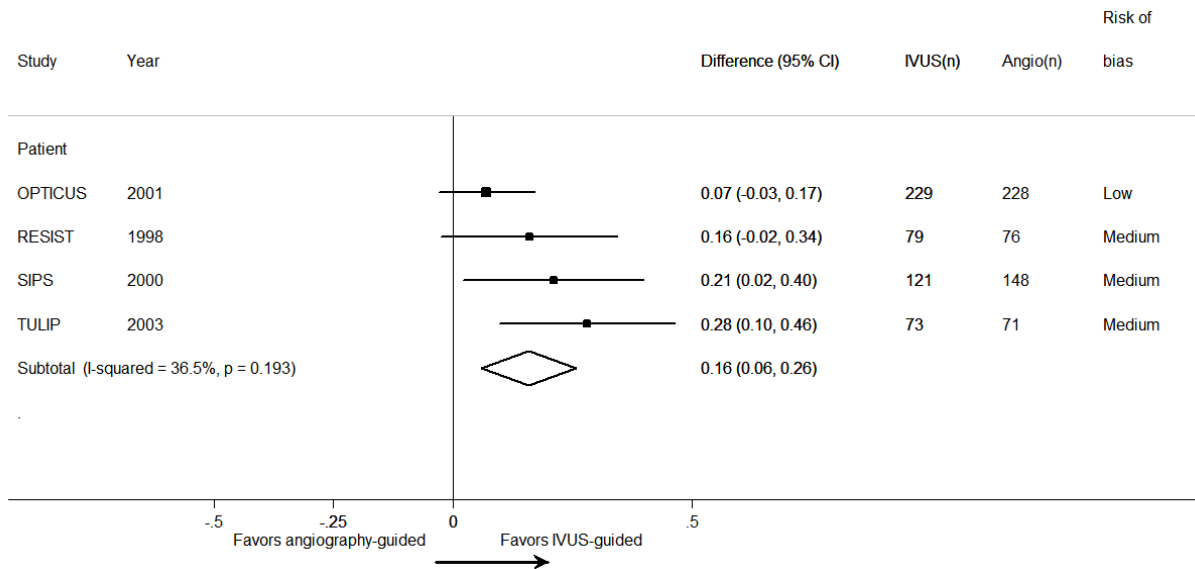
A confidence interval that crosses 0 indicates no significant mean difference; values >0 indicate that a larger minimal lumen diameter was achieved in the IVUS group over the angiography alone group.

### Medium-Term (Up to 1 Year) MLD

Meta-analysis of the net changes in MLD between IVUS-guided and angiography-guided stent placement groups, from baseline to medium-term (up to 1 year), across four RCTs<sup>23,29,31,33</sup> found a significant favorable effect with IVUS over angiography alone (Figure 5). No sensitivity analysis by risk of bias was performed due to the small number of available studies per subgroup. Meta-analysis of the nonrandomized studies (two patient-level<sup>35,43</sup> and four studies reporting five sets of lesion-level data<sup>34,39,45,46</sup>) revealed no significant difference between groups (Figure 6).

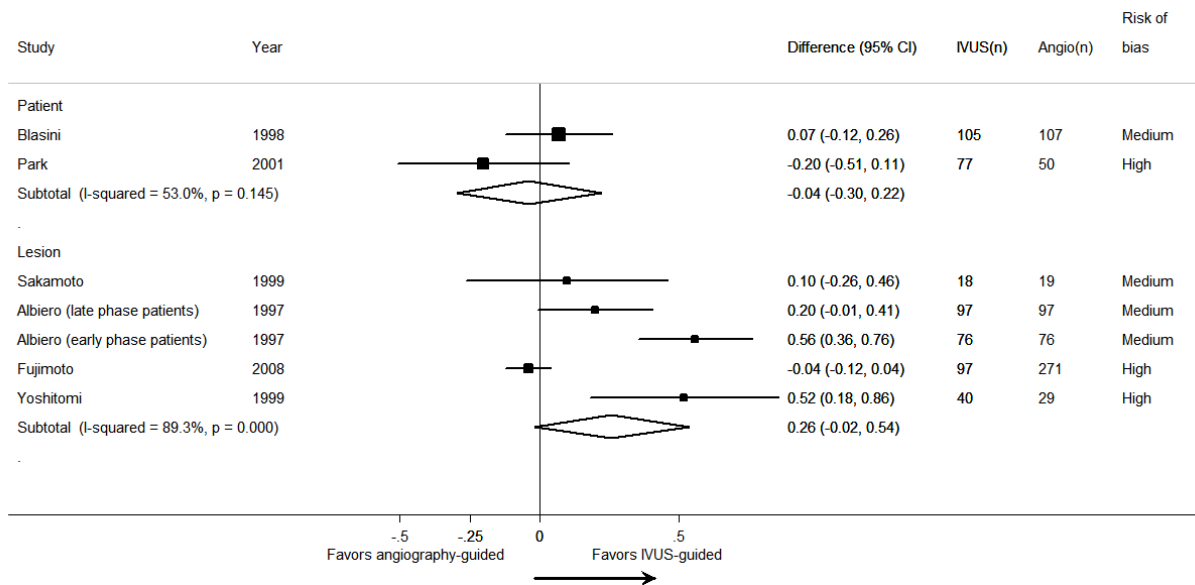
In summary, the available RCTs and observational data demonstrated conflicting results in the medium term (up to 1 year), and therefore, we cannot draw a conclusion as to whether the use of IVUS significantly increases MLD during medium-term followup.

**Figure 5. RCTs of medium-term minimal lumen diameter: forest plot**



Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n = number  
 Notes: Estimates favoring IVUS are in the direction of the arrow, in contrast to Figures 7-10 on diameter stenosis.  
 A confidence interval that crosses 0 indicates no significant mean difference; values >0 indicate that a larger minimal lumen diameter was achieved in the IVUS group over angiography alone group.

**Figure 6. Nonrandomized comparative studies of medium-term minimal lumen diameter: forest plot**



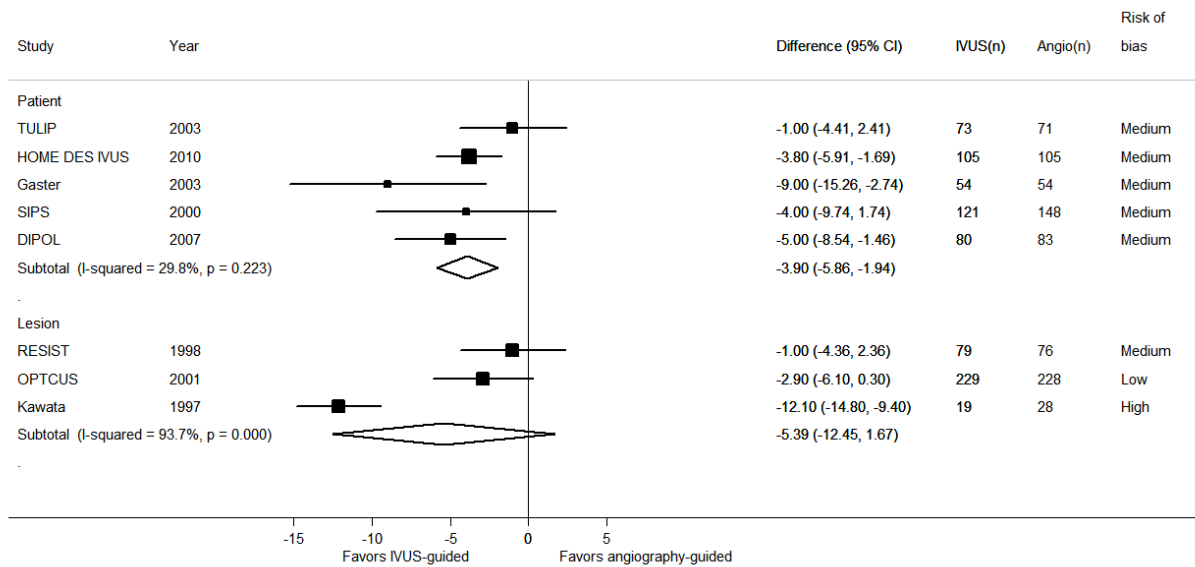
Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n = number  
 Notes: Estimates favoring IVUS are in the direction of the arrow, in contrast to Figures 7-10 on diameter stenosis.  
 A confidence interval that crosses 0 indicates no significant mean difference; values >0 indicate that a larger minimal lumen diameter was achieved in the IVUS group over angiography alone group.

## In-Hospital Diameter Stenosis

Among eight RCTs,<sup>23,25-29,31,33</sup> meta-analysis of the five RCTs<sup>23,25-27,31</sup> reporting data by patient revealed a significant difference in the net changes in percent diameter stenosis, indicating a favorable effect for IVUS-guided over angiography-guided stent placement (Figure 7). Meta-analysis of either the three RCTs that reported lesion-level data,<sup>28,29,33</sup> or the 14 nonrandomized comparative studies that reported 16 data points (either at the patient- or lesion-level),<sup>34,35,37-42,45-48,52,55</sup> revealed consistent small gains favoring IVUS, but there was no significant difference between groups (Figures 7 and 8).

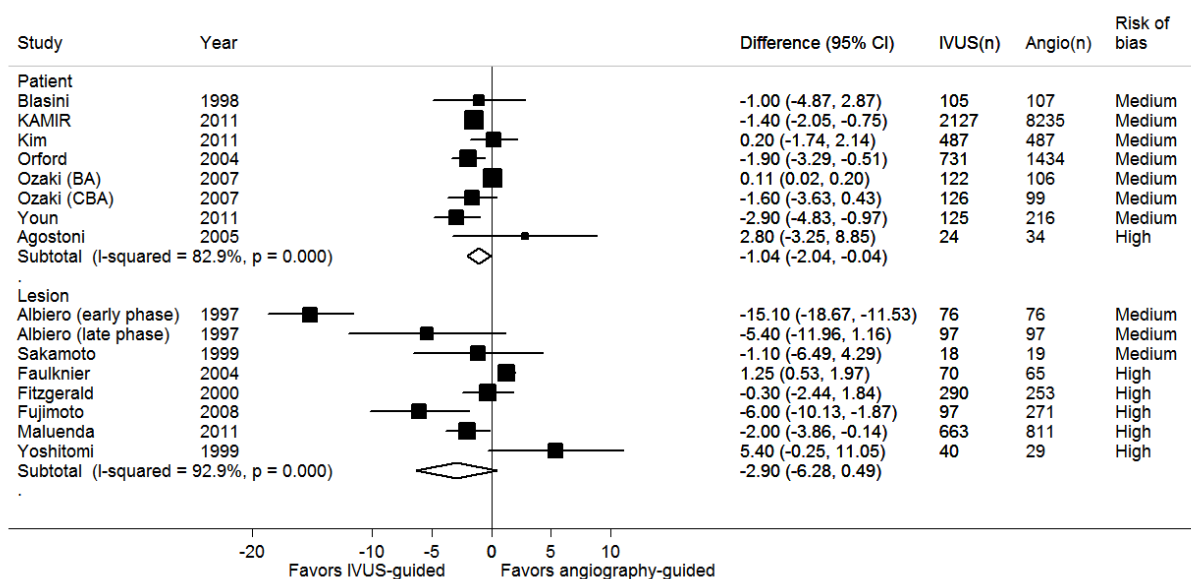
In summary, the available studies demonstrated conflicting results, and we therefore cannot draw a conclusion as to whether the use of IVUS significantly decreases stenosis during postprocedural period.

**Figure 7. RCTs of in-hospital percent diameter stenosis: forest plot**



Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n = number  
 Note: A confidence interval that crosses 0 indicates no significant mean difference.

**Figure 8. Nonrandomized comparative studies of in-hospital percent diameter stenosis: forest plot**

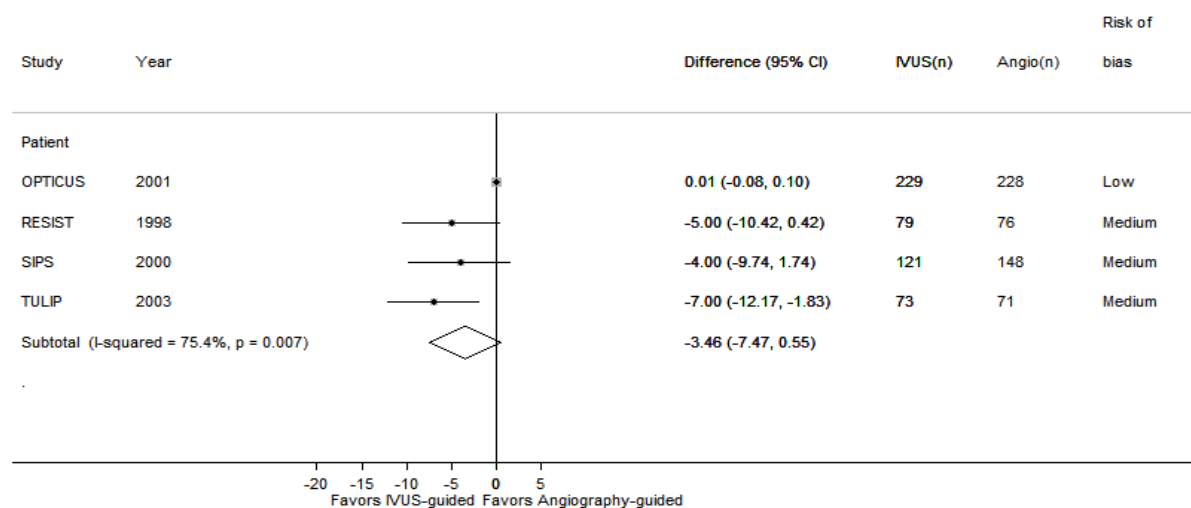


Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n = number.  
 Note: A confidence interval that crosses 0 indicates no significant mean difference.

Meta-analysis of the net changes in percent diameter stenosis between the IVUS-guided stenting group and the group receiving stenting guided by angiography alone, during medium-term followup, across four RCTs<sup>23,29,31,33</sup> and four nonrandomized studies (reporting five sets of lesion-level data)<sup>34,39,45,46</sup> revealed no significant difference between groups (Figures 9 and 10). The lone nonrandomized study (Blasini, 1998) analyzing data by patient reported a significant favorable effect of IVUS-guided stenting over angiography alone (Figure 10).<sup>35</sup>

In summary, the available studies demonstrated no significant difference between groups for the outcome of percent diameter stenosis in the medium term (up to 1 year).

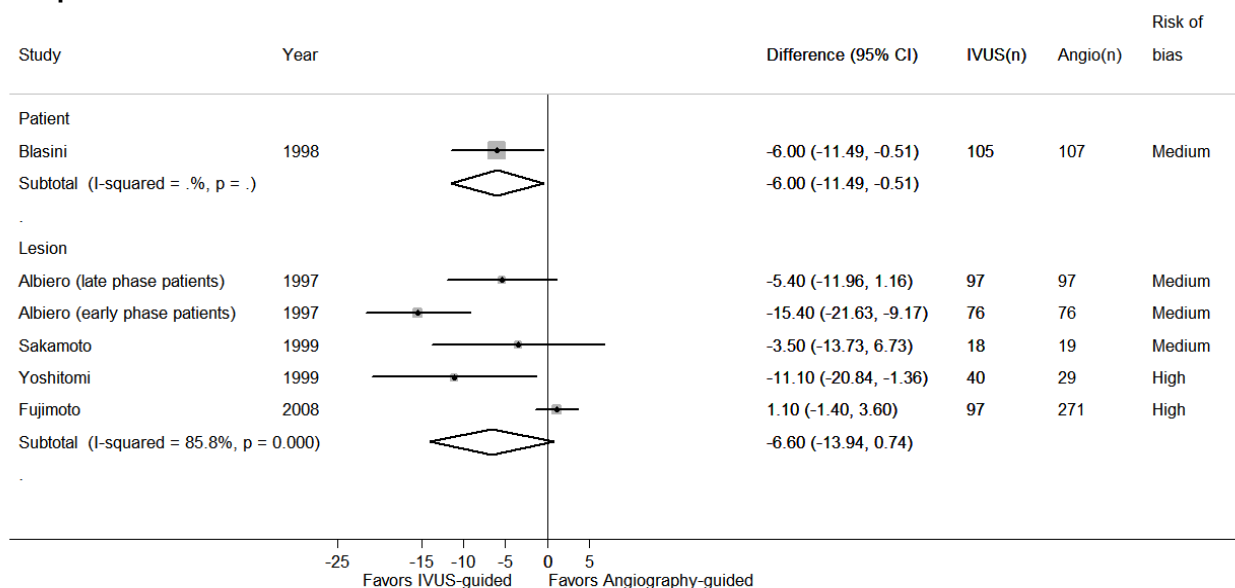
**Figure 9. RCTs of medium-term percent diameter stenosis: forest plot**



Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n=number  
 Note: A confidence interval that crosses 0 indicates no significant mean difference.



**Figure 10. Nonrandomized comparative studies of medium-term percent diameter stenosis: forest plot**



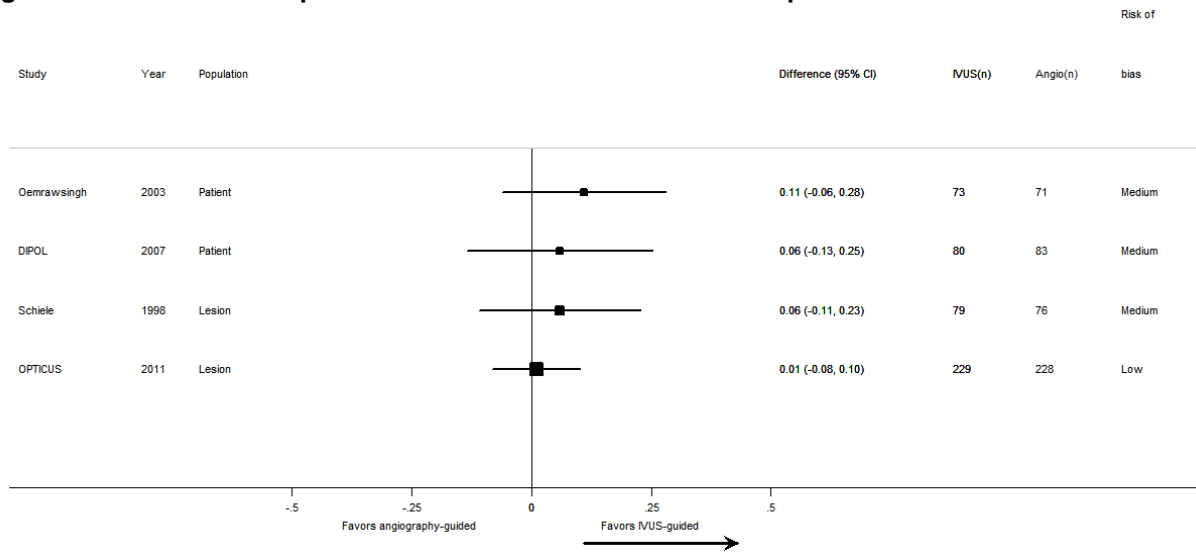
Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n = number  
 Note: A confidence interval that crosses 0 indicates no significant mean difference.

### In-Hospital Reference Vessel Diameter

Small nonsignificant gains favoring IVUS were found in the net changes in reference vessel diameter between the IVUS-guided and angiography guided stent placement groups, from baseline to postprocedure, in the four RCTs examined (Figure 11).<sup>26,29,31,33</sup> No meta-analysis was performed due to the small number of RCTs per category (patient- or lesion-level). Of the nine nonrandomized comparative studies,<sup>34,35,38,39,41,45,48,50,55</sup> the five reporting six sets of lesion-level data<sup>34,38,39,45,50</sup> revealed a significant difference indicating a favorable effect for IVUS-guided stenting over stent procedures guided by angiography alone (Figure 12). Meta-analysis of the four patient-level nonrandomized comparative studies<sup>35,41,48,55</sup> revealed no statistically significant difference between groups (Figure 12).

In summary, the available studies demonstrated conflicting results, and we therefore cannot draw a conclusion as to whether the use of IVUS significantly changes reference vessel diameter during the postprocedural period.

**Figure 11. RCTs of in-hospital reference vessel diameter: forest plot**

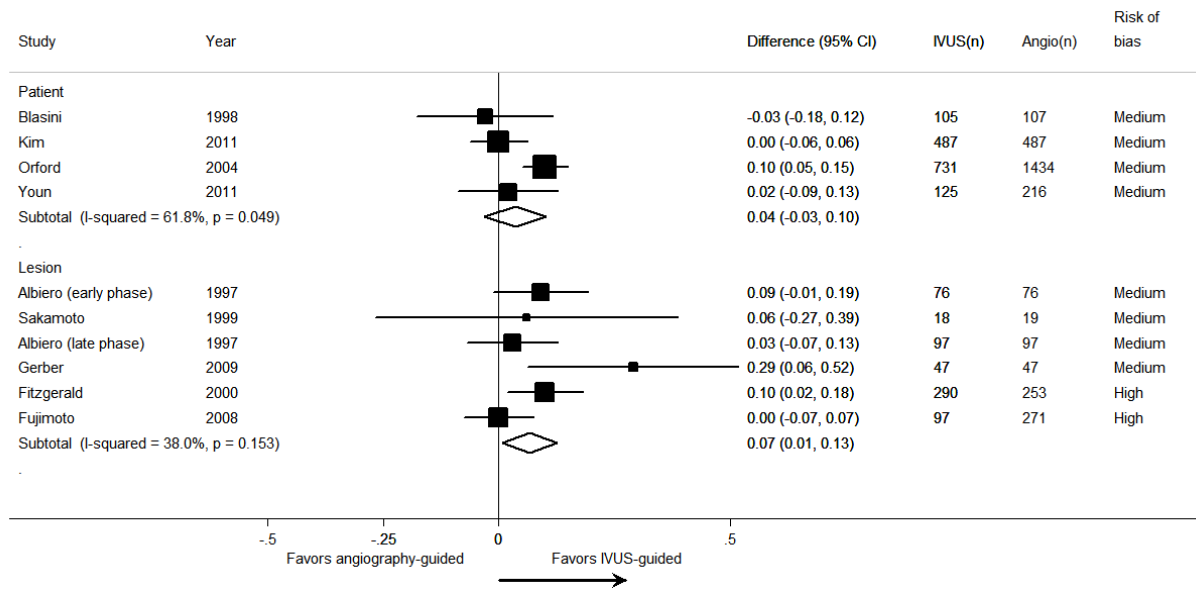


Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n = number

Notes: Estimates favoring IVUS are in the direction of the arrow, in contrast to Figures 7-10 on diameter stenosis.

A confidence interval that crosses 0 indicates no significant mean difference.

**Figure 12. Nonrandomized comparative studies of in-hospital reference vessel diameter: forest plot**



Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n = number

Notes: Estimates favoring IVUS are in the direction of the arrow, in contrast to Figures 7-10 on diameter stenosis.

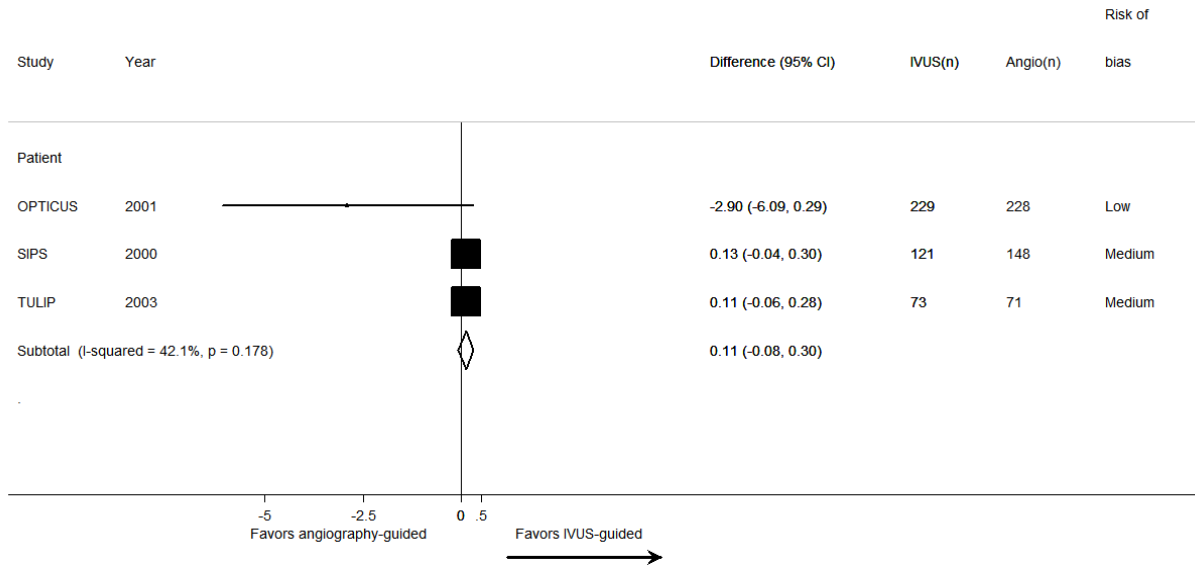
A confidence interval that crosses 0 indicates no significant mean difference.

### Medium-Term (Up to 1 Year) Reference Vessel Diameter

Meta-analysis of the net changes in reference diameter between the IVUS-guided and angiography-guided stent placement groups, from baseline to medium-term, across three

RCTs<sup>23,29,31</sup> and three nonrandomized comparative studies (reporting four lesion-level data sets),<sup>34,39,45</sup> revealed no significant difference between groups (Figures 13 and 14). The only nonrandomized comparative study analyzing data by patient reported no significant difference between groups.<sup>35</sup>

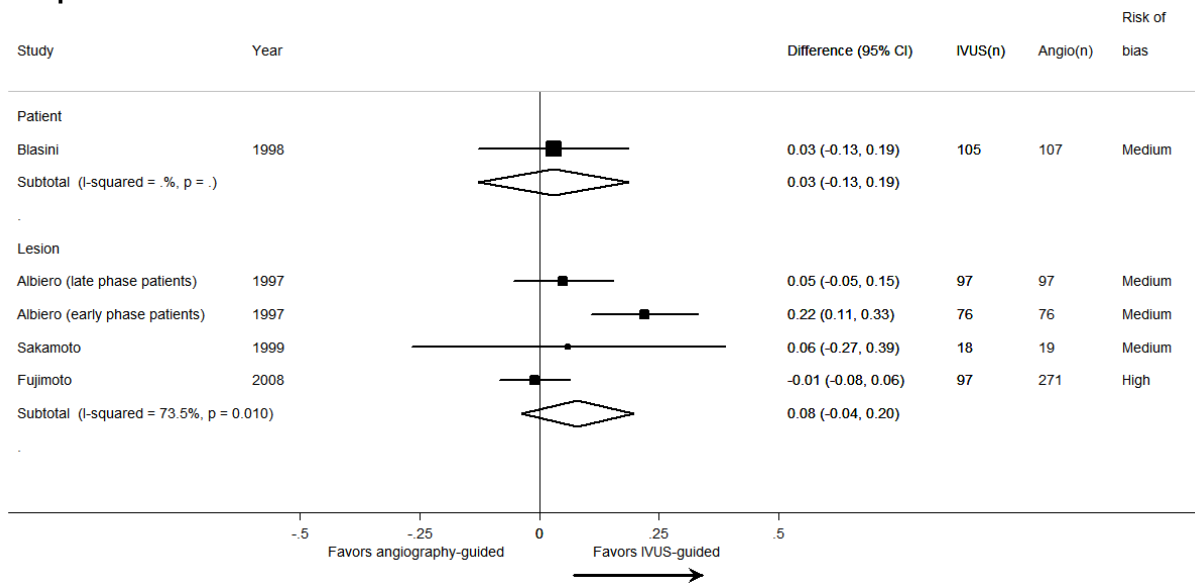
**Figure 13. RCTs of medium-term reference vessel diameter: forest plot**



Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n = number  
 Notes: Estimates favoring IVUS are in the direction of the arrow, in contrast to Figures 7-10 on diameter stenosis.

A confidence interval that crosses 0 indicates no significant mean difference.

**Figure 14. Nonrandomized comparative studies of medium-term reference vessel diameter: forest plot**



Angio = angiography; CI = confidence interval; IVUS = intravascular ultrasound; n = number  
 Notes: Estimates favoring IVUS are in the direction of the arrow, in contrast to Figures 7-10 on diameter stenosis.  
 A confidence interval that crosses 0 indicates no significant mean difference.

In summary, the available studies demonstrated no significant difference between groups for the outcome of reference vessel diameter in the medium term (up to 1 year).

### **Late Lumen Loss**

Meta-analysis of three RCTs<sup>23,29,31</sup> (summary mean difference in late lumen loss -0.001 mm [95% CI -1.13, 0.13; NS]) and one nonrandomized comparative study<sup>45</sup> revealed no significant difference between groups in late lumen loss (figure not displayed).

Across all QCA outcomes, the available studies demonstrated either conflicting or nonsignificant results, and we therefore cannot draw a conclusion as to whether the use of IVUS significantly changes QCA outcomes at all time points.

### **Stent-Related Outcomes**

#### **In-Hospital and Medium-Term Restenosis**

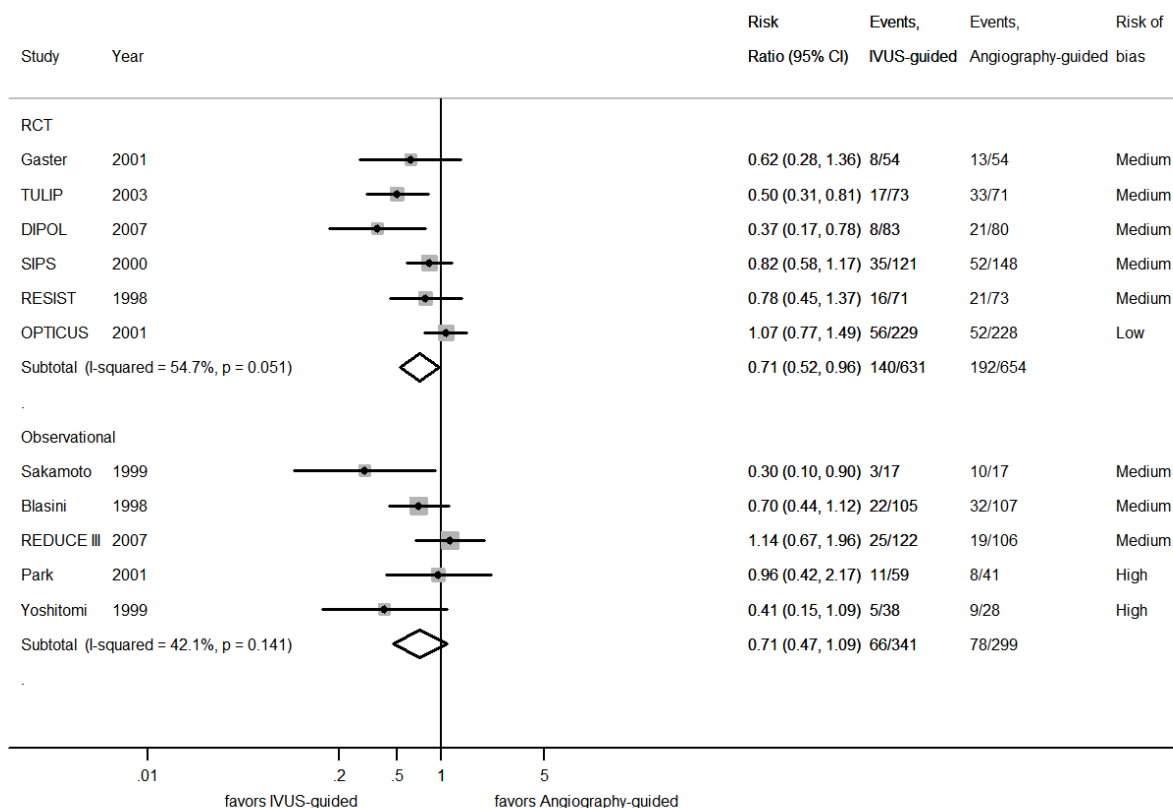
In-hospital restenosis rates were not significantly different between groups in one RCT<sup>29</sup> and three nonrandomized comparative studies.<sup>34,43,53</sup>

Six RCTs provided data for binary restenosis at 6-month followup. Meta-analysis of six RCTs<sup>23,24,26,29-31,33</sup> revealed a significantly lower risk (29%) of restenosis in the IVUS-guided group compared with the angiography alone group (Figure 15). Two small sample size RCTs found a statistically significant effect favoring IVUS use, while the remaining RCTs, including two of a large sample size, did not. A meta-analysis of five nonrandomized comparative studies (data by patients)<sup>35,42,43,45,46</sup> found a 29 percent lower (though nonsignificantly so) risk of restenosis in the IVUS-guided group compared with the angiography alone group (Figure 15).

We did not identify any studies that reported restenosis rates with greater than 1 year of followup.

In summary, the available studies demonstrated that the use of IVUS significantly decreases binary restenosis rates during medium-term followup.

**Figure 15. Medium-term restenosis: forest plot**



CI = confidence interval; IVUS = intravascular ultrasound

### Stent Thrombosis

No RCTs reported data on in-hospital subacute stent thrombosis. Of the three nonrandomized comparative studies that reported data on in-hospital subacute stent thrombosis, no instance of subacute stent thrombosis was reported in two,<sup>34,52</sup> while the other reported no statistically significant difference between groups.<sup>48</sup>

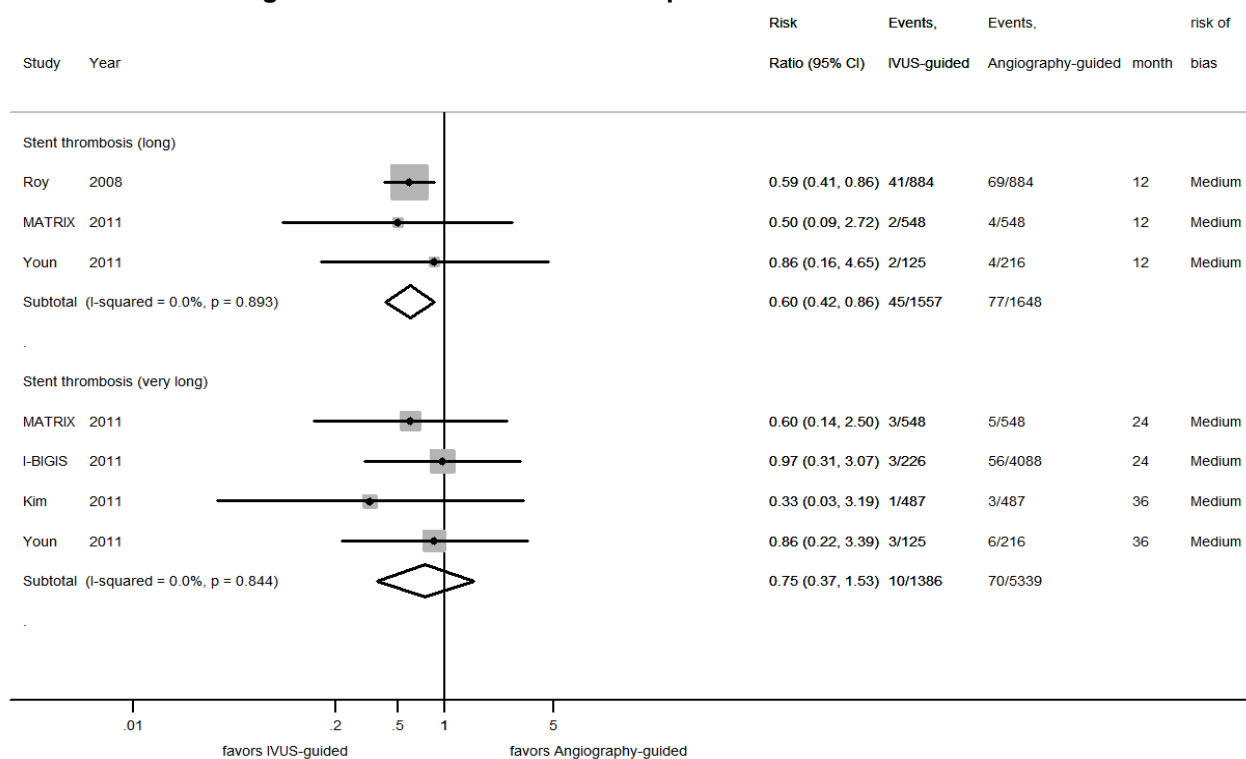
Stent-related thromboses at 30 days were reported in six nonrandomized comparative studies; five studies reported either no events or no difference between groups,<sup>40,52-55</sup> while the lone study identified a significantly higher incidence of cumulative stent thrombosis in the IVUS-guided group compared with the angiography alone group.<sup>44</sup>

Of the two RCTs that provided data for stent thrombosis in the medium duration timeframe,<sup>26,32</sup> one reported no events in either of the groups,<sup>26</sup> and the other reported no significant difference between groups at 1 year followup.<sup>32</sup> No meta-analysis was performed for the RCTs due to the small number of studies. Of the five nonrandomized comparative studies that provided data on stent thrombosis,<sup>39,40,44,54,55</sup> one reported no events in either of the groups at 8 months (lesion-level),<sup>39</sup> one reported no difference at 6 months,<sup>40</sup> two reported no difference at 1 year,<sup>54,55</sup> and one reported a significant favorable effect of IVUS-guided stenting over stents placed using angiography alone, over 1 year of followup.<sup>44</sup>

One RCT<sup>27</sup> and four nonrandomized comparative studies<sup>48,53-55</sup> reported no significant difference in stent thrombosis between groups in the long-term followup.

A meta-analysis of nonrandomized studies found a significant decrease in the medium term (up to 1 year); however, this significance was lost after 2 years (Figure 16).

**Figure 16. Medium- and long-term stent thrombosis: forest plot**



CI = confidence interval; IVUS = intravascular ultrasound

Note: Long stent thrombosis indicates stent thrombosis occurring within 1 year; very long stent thrombosis indicates stent thrombosis occurring after 1 year.

In summary, a small number of studies indicated a decreased risk of stent thrombosis in the medium and long terms favoring IVUS use.

### Periprocedural Complications

Periprocedural complications (reported in three RCTs) during stent placement included: prolonged spasm after stent implantation (only in the IVUS-guided stent placement group);<sup>29</sup> more vessel dissection requiring additional therapy in the IVUS group relative to the angiography alone group;<sup>32</sup> and vessel dissection, intima peeling off the lumen, suboptimal stenting results, and nonQ wave MI (only in the angiography alone group).<sup>28</sup> Among the nonrandomized studies, four reported no significant differences in dissection or abrupt closure between groups,<sup>34,44-46</sup> though one reported a significantly lower rate of abrupt closure with IVUS compared with angiography alone.<sup>36</sup>

In summary, a small number of studies indicated no significant differences between groups with respect to periprocedural complications.

### Patient-Centered Outcomes

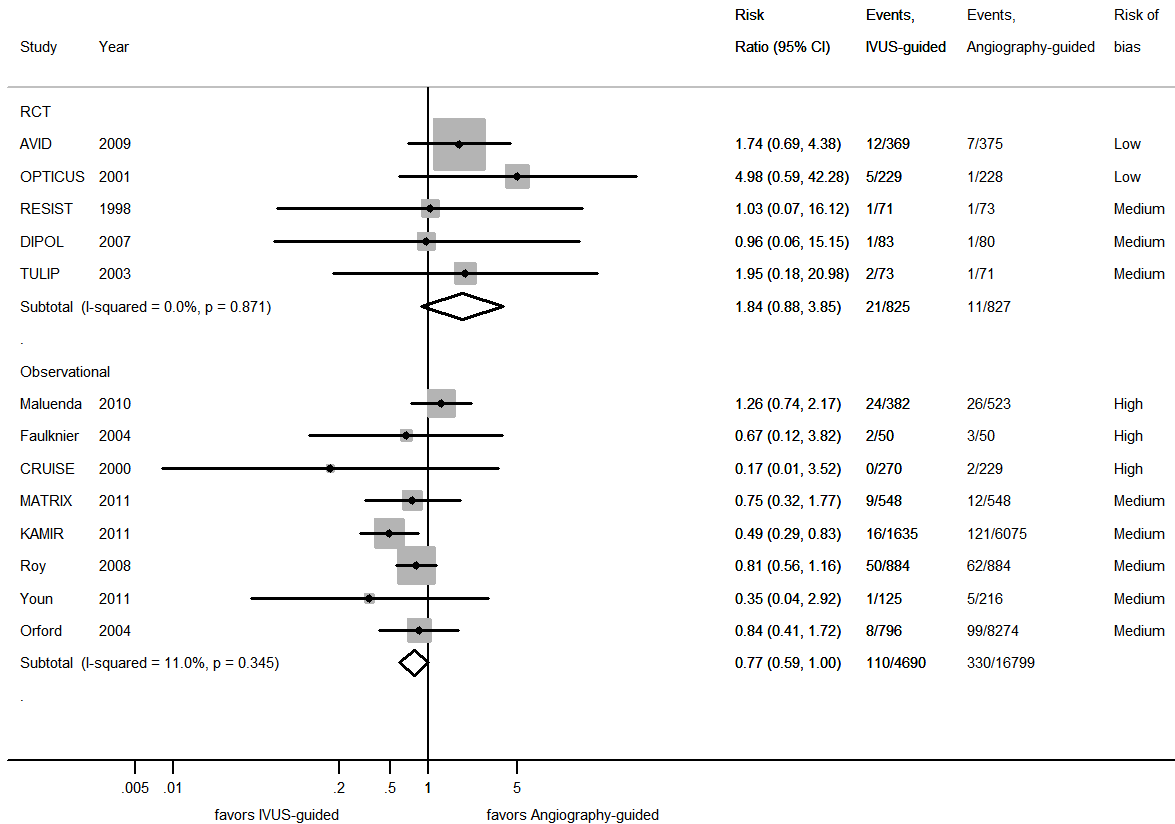
#### All-Cause Mortality

Among the eight studies (3 RCTs,<sup>23,25,29</sup> and 5 nonrandomized studies<sup>44,45,53-55</sup>) no in-hospital all-cause mortality was observed in RCTs. No in-hospital all-cause mortality was observed in one of the observational studies as well,<sup>45</sup> while four nonrandomized comparative studies

reported no statistically significant difference between groups.<sup>44,53-55</sup> The available studies showed no significant difference for all-cause mortality during in-hospital stay.

In the medium timeframe, meta-analysis of five RCTs<sup>26,29,31-33</sup> and eight nonrandomized comparative studies<sup>37,38,40,41,44,52,54,55</sup> found no statistical significance in the risk of all-cause mortality between groups (Figure 17). The meta-analysis of RCTs revealed 84 percent higher risk in mortality with IVUS use as compared with angiography alone, while the meta-analysis of nonrandomized studies found 23 percent lower risk in mortality with IVUS versus angiography alone during stent deployment.

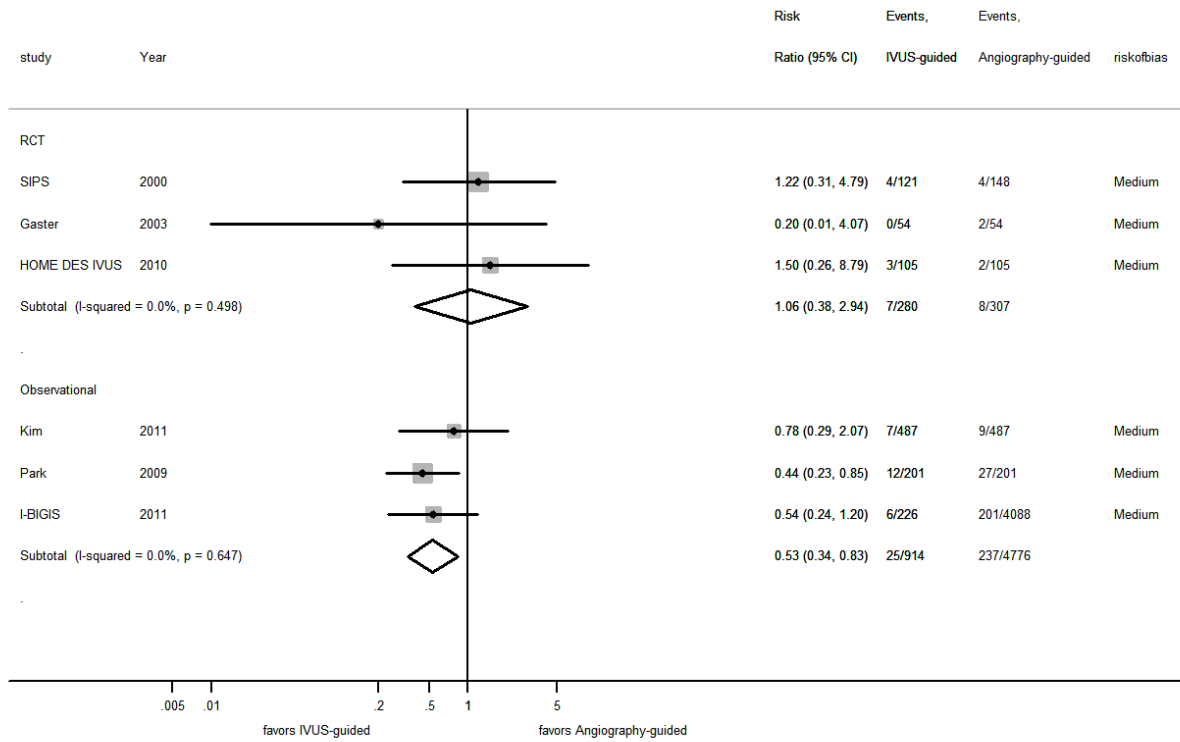
**Figure 17. Medium-term all-cause mortality: forest plot**



CI = confidence interval; IVUS = intravascular ultrasound

With regards to long-term followup, meta-analysis of three RCTs<sup>23,25,27</sup> found a 6 percent higher (though nonsignificantly so) risk of all-cause mortality with IVUS-guided stenting than with angiography-guided stent placement (Figure 18). The meta-analysis of three nonrandomized comparative studies<sup>48,49,53</sup> found a statistically significant, 47 percent lower risk of all-cause mortality with IVUS-guided stenting than with angiography-guided stent placement during long-term followup (Figure 18). Of the three nonrandomized comparative studies that evaluated this outcome,<sup>48,49,53</sup> two reported a point estimate indicating a favorable effect of IVUS-guided stent placement, but statistical significance was reached in only one.<sup>49</sup> In summary, the available studies (across RCTs and nonrandomized studies) demonstrated either conflicting or nonsignificant results, and we therefore cannot draw a conclusion as to whether the use of IVUS significantly decreased all-cause mortality.

**Figure 18. Long-term all-cause mortality: forest plot**



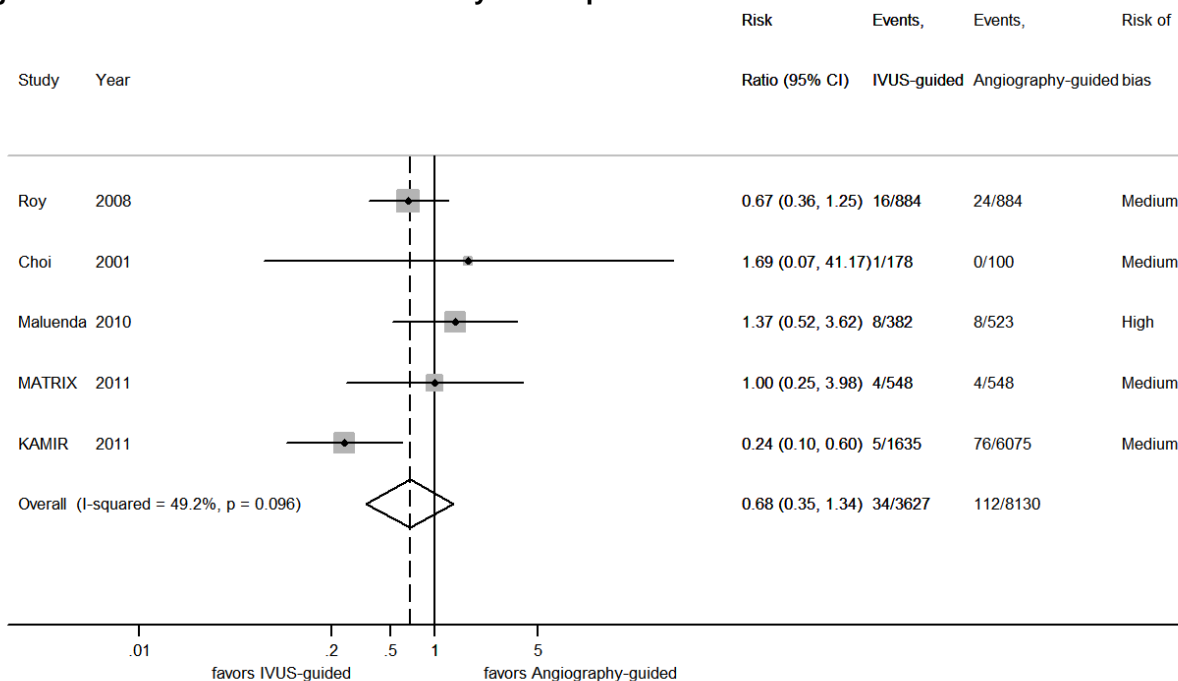
CI = confidence interval; IVUS = intravascular ultrasound

### Cardiac Mortality

We identified no RCT that reported cardiac mortality in the medium timeframe. Meta-analysis of five nonrandomized comparative studies<sup>36,40,44,52,54</sup> demonstrated a 32 percent lower risk, but no statistical significance in the risk of cardiac mortality between groups (Figure 19).



**Figure 19. Medium-term cardiac mortality: forest plot**



CI = confidence interval; IVUS = intravascular ultrasound

None of the three RCTs reported data for cardiac mortality. One retrospective nonrandomized comparative study enrolling 975 patients reported a significantly lower rate of 3-year cardiac mortality in the IVUS-guided compared with the angiography-guided stent placement group (RR 0.32; 95% CI 0.18, 0.56;  $p < 0.0001$ ).<sup>49</sup> Another study analyzing registry data of 1,504 patients reported no difference between groups at 2 years (1% vs. 1.8%;  $p = 0.28$ ).<sup>54</sup>

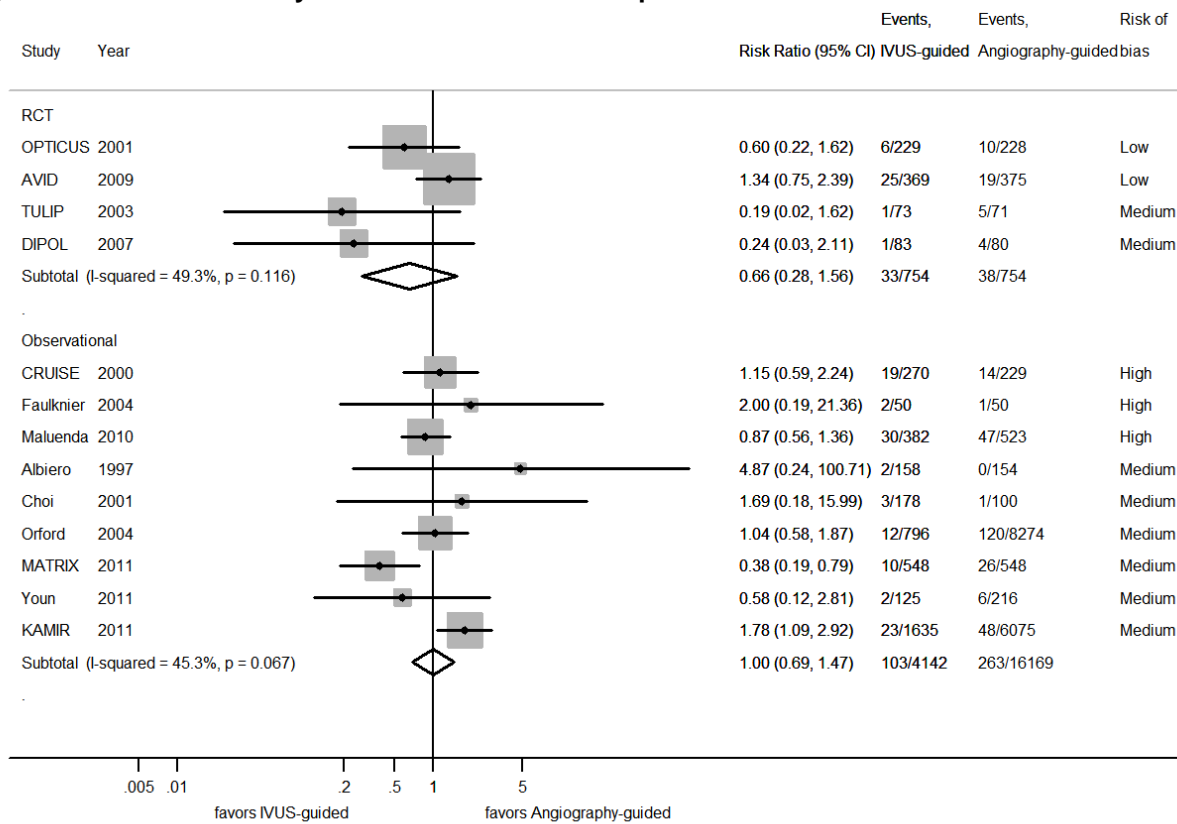
In summary, a small number of studies indicated a decrease in the risk of cardiac mortality with the use of IVUS, but without statistically significant differences between groups.

### Myocardial Infarction

One RCT reported no instances of in-hospital acute MI<sup>25</sup> while the other two RCTs,<sup>23,29</sup> and two of the nonrandomized comparative studies<sup>34,45</sup> found no statistically significant difference between groups. The remaining nonrandomized comparative study reported significantly lower rates of Q-wave MI in the IVUS than in the angiography alone group (0.1% in the IVUS group vs. 0.9% in the angiography alone group;  $p < 0.02$ ).<sup>44</sup> Two additional nonrandomized studies<sup>52,53</sup> found no statistically significant difference in acute MI between groups at 30 days. The remaining nonrandomized comparative study reported significantly lower rates of MI in the IVUS than in the angiography alone group at 30 days (adjusted hazard ratio [HR] 0.24; 95% CI 0.07, 0.77;  $p = 0.02$ ).<sup>54</sup> The available studies showed no significant difference for MI during in-hospital stay.

Meta-analysis of four RCTs<sup>26,29,31,32</sup> (34% lower risk) and nine nonrandomized comparative studies<sup>34,36-38,40,41,52,54,55</sup> (no difference) that provided data for MI in the medium timeframe found no statistical significance in the risk of MI between groups (Figure 20).

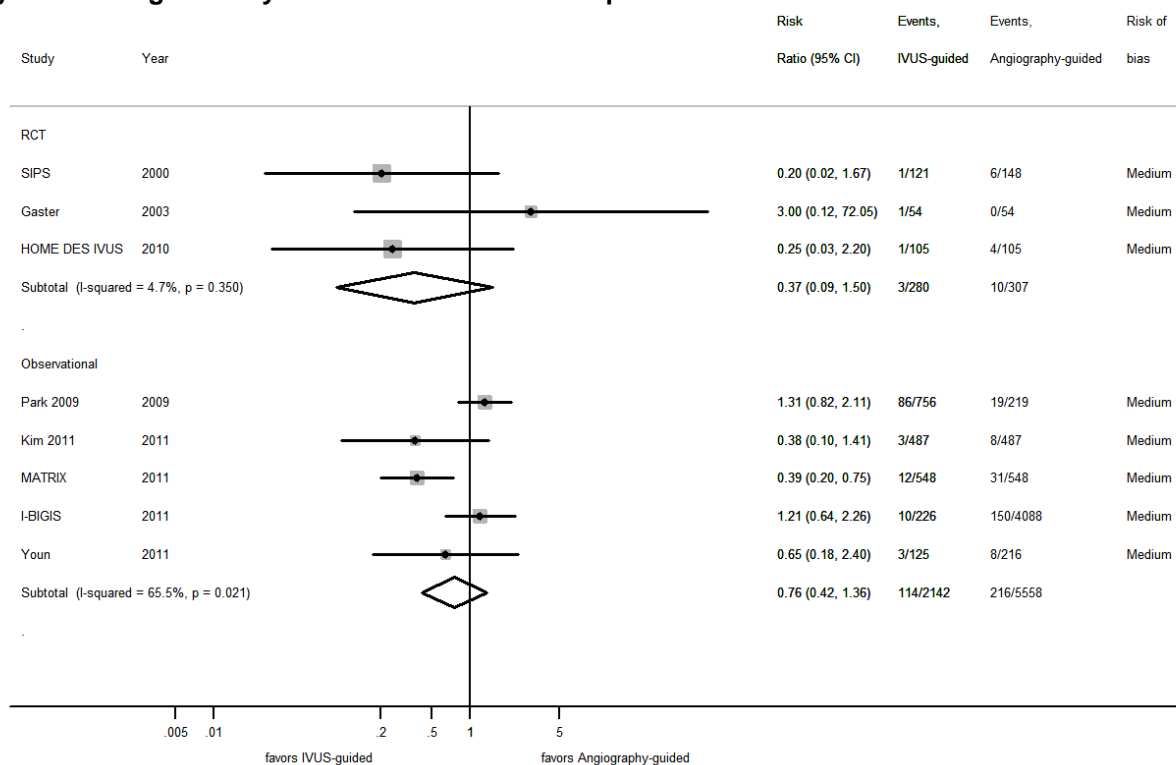
**Figure 20. Medium-term myocardial infarction: forest plot**



CI = confidence interval; IVUS = intravascular ultrasound.

During long-term followup, meta-analysis of the three included RCTs<sup>23,25,27</sup> found 63 percent lower risk of MI in the IVUS group compared with angiography alone group, but this did not reach statistical significance. The meta-analysis of five nonrandomized comparative studies also found no significant difference in the risk between the IVUS and angiography alone groups (Figure 21).<sup>48,49,53-55</sup> In summary, the available studies showed no significant difference for MI during medium- and long-term followup.

**Figure 21. Long-term myocardial infarction: forest plot**



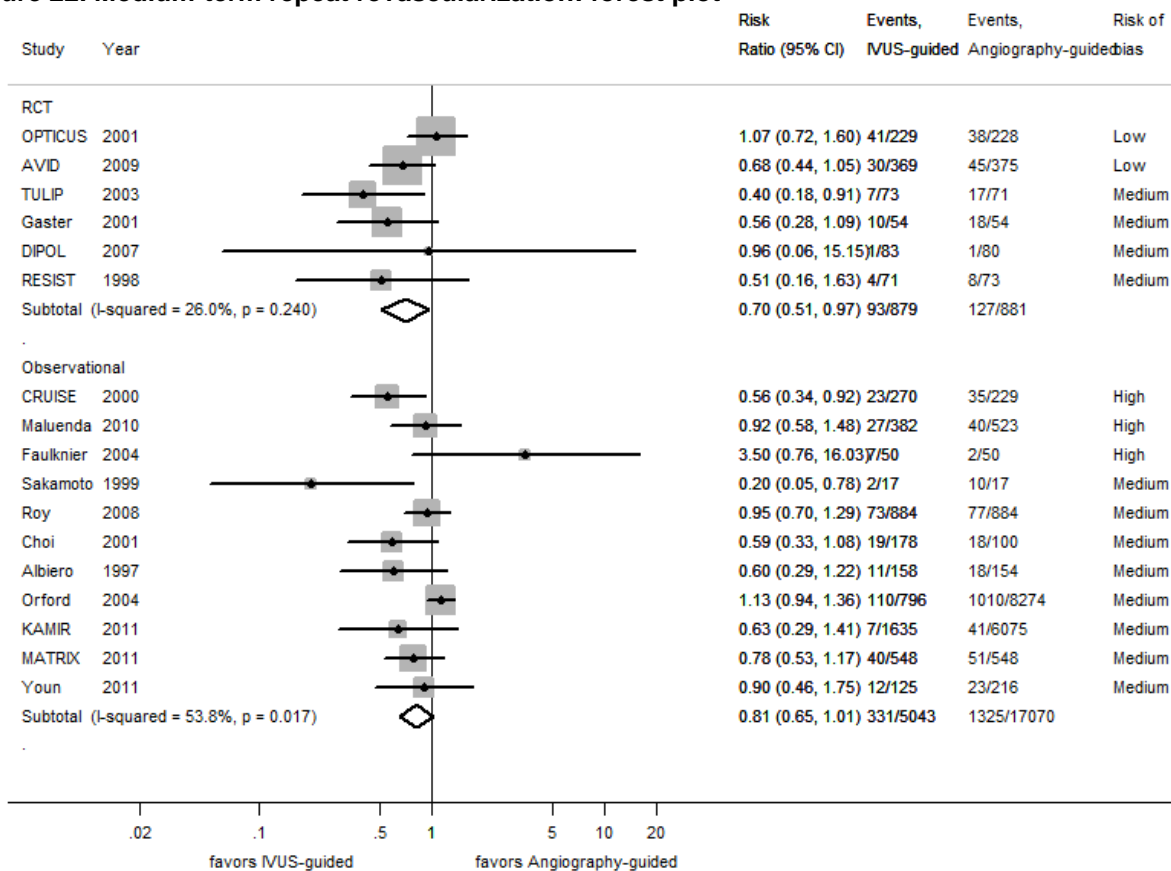
CI = confidence interval; IVUS = intravascular ultrasound.

### Repeat Revascularization

Data on repeat revascularization during in-hospital stay was reported in five RCTs<sup>23,24,26,29,31</sup> and in five nonrandomized comparative studies.<sup>34,44,45,53,54</sup> Meta-analysis of all five RCTs revealed a nonstatistically significant decrease in repeat revascularization during in-hospital stay in the IVUS group compared with the angiography alone group (summary RR 0.50; 95% CI 0.20, 1.27), without statistical heterogeneity ( $I^2 = 0\%$ ) (figure not displayed). Among the nonrandomized comparative studies, two reported no patients undergoing repeat revascularization,<sup>34,45</sup> two reported similar rates of repeat revascularization within 30 days,<sup>53,54</sup> and one reported similar rates in the need for emergent CABG in both groups.<sup>44</sup> The available studies showed no significant difference for repeat revascularization during in-hospital stay.

During medium-term followup, meta-analysis of all six RCTs<sup>24,26,29,31-33</sup> with almost 1,800 patients revealed 30 percent significantly lower risk of clinically driven repeat revascularization among patients who received IVUS-guided stent placement compared with those who received stents guided by angiography alone (Figure 22). A meta-analysis of 11 of the nonrandomized comparative studies (data by 22,000 patients)<sup>34,36-38,40,41,44,45,52,54,55</sup> found 19 percent lower risk, but no statistical significance in the risk of repeat revascularization between groups (Figure 22).

**Figure 22. Medium-term repeat revascularization: forest plot**

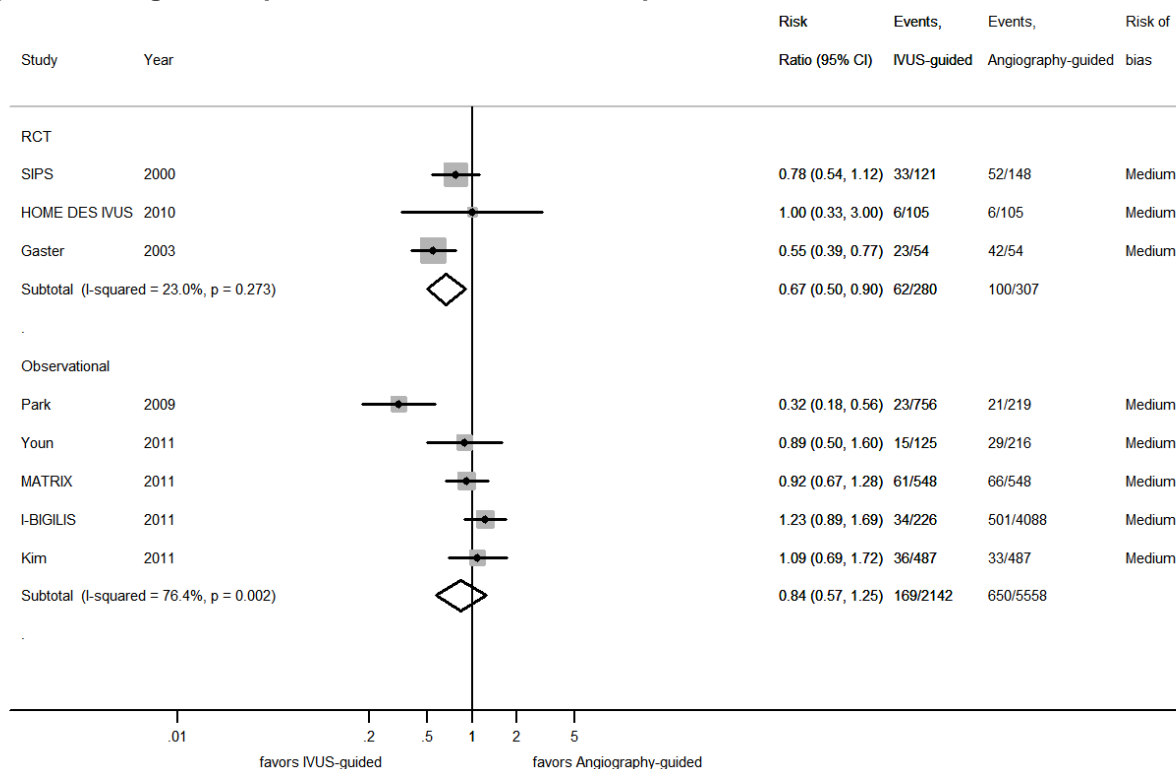


CI = confidence interval; IVUS = intravascular ultrasound

During long-term followup, meta-analysis of the three included RCTs<sup>23,25,27</sup> found a significantly 33 percent lower risk of repeat revascularization among patients who received IVUS-guided stent placement compared with those who received stents guided by angiography alone. The meta-analysis of five nonrandomized comparative studies that provided data for repeat revascularization, found no significant difference between groups (Figure 23).<sup>48,49,52,54,55</sup>

In summary, the available studies demonstrated a significant reduction in repeat revascularization (defined heterogeneously across studies) with IVUS over angiography alone during medium- and long-term followup.

**Figure 23. Long-term repeat revascularization: forest plot**



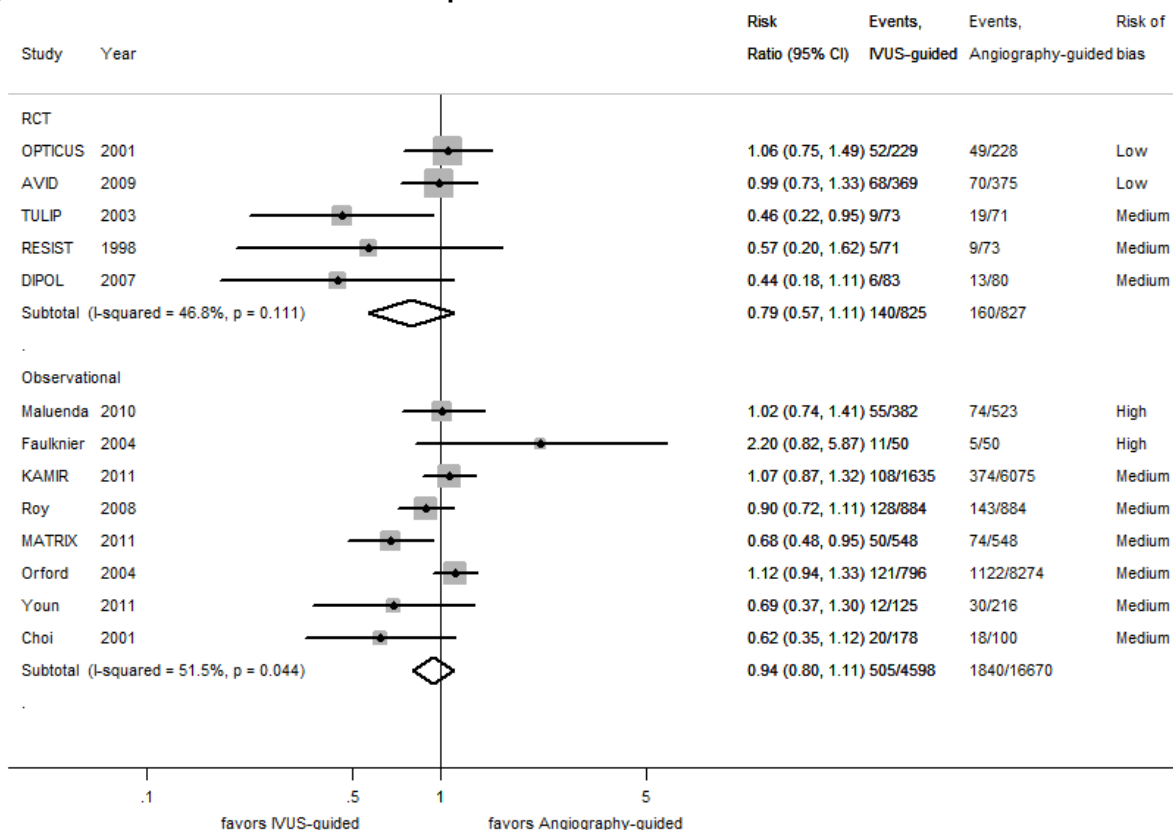
CI = confidence interval; IVUS = intravascular ultrasound

## MACE

The overall rates of in-hospital MACE and its individual components of death, MI, and repeat revascularization were reported as similar between groups in two RCTs.<sup>29,31</sup> Three nonrandomized comparative study reported similar findings,<sup>40,53,55</sup> while one other identified a significantly lower incidence of MACE in the IVUS group compared with the angiography alone group.<sup>44</sup> The available studies showed no significant difference for MACE during in-hospital stay.

Meta-analysis of five RCTs<sup>26,29,31-33</sup> revealed a nonsignificantly lower risk (21%) of MACE during medium-term followup (up to 1 year), and eight nonrandomized studies<sup>36,37,40,41,44,52,54,55</sup> found no significant difference in the risk of MACE between IVUS-guided stenting and stent placement guided by angiography alone (Figure 24). The definition of MACE varied considerably among studies (see Appendix C).

**Figure 24. Medium-term MACE: forest plot**

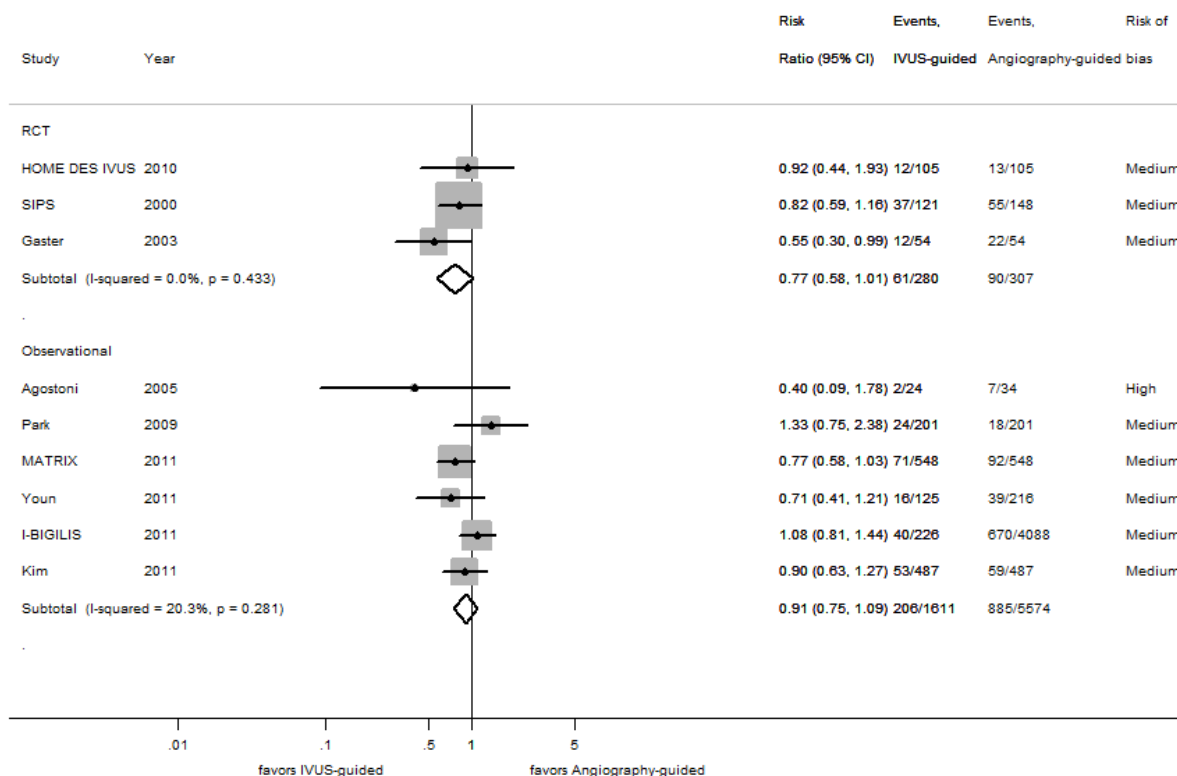


CI = confidence interval; IVUS = intravascular ultrasound; MACE = major adverse cardiac event

Meta-analysis of all included studies with long-term followup (>1 year) found a lower risk of MACE (23% lower risk in three RCTs<sup>25,27,30</sup> and 9% lower risk in six nonrandomized studies<sup>47-49,53-55</sup>) with IVUS over angiography alone; however, the results were not statistically significant (Figure 25).

In summary, across all time points, the available studies indicated no significant difference for the outcome of MACE (defined heterogeneously across studies) between groups.

**Figure 25. Long-term MACE: forest plot**



CI = confidence interval; IVUS = intravascular ultrasound; MACE = major adverse cardiac event

## Other Intravascular Diagnostic Techniques Compared With Angiography Alone

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 could be drawn from this single high-risk-of-bias study.<sup>19</sup> 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, and patient-centered outcomes?

### Key Points

- There is insufficient evidence regarding the adjunctive use of intravascular diagnostic techniques immediately post-procedure, to evaluate the success of stent placement.
- Two studies, both evaluating IVUS were rated as being at a high risk of bias.
- No studies evaluated FFR or any other intravascular diagnostic technique on the success of stenting immediately after the procedure.

## Summary of Evidence

There is insufficient evidence regarding the comparisons of interest in this Key Question, as data were drawn from two studies, both evaluating IVUS and rated as being at a high risk of bias, with each reporting on two different types of outcomes at different time points. There is insufficient evidence for any intravascular diagnostic technique, as none of the reviewed studies evaluated the effect of FFR or any other intravascular diagnostic technique on the success of stent placement immediately post- procedure.

## Available Evidence

Two retrospective studies addressed this Key Question.<sup>57,58</sup> Neither of these studies adjusted for potential confounders.

Nasu 2004 compared the use of IVUS with angiography in patients with either *de novo* or restenotic lesions who had a stand-alone directional coronary atherectomy (DCA) without angioplasty.<sup>57</sup> The study did not provide baseline characteristics for the two groups separately. IVUS assessments were obtained for 38 patients with 38 lesions. This was compared with 53 patients (inferred from paper, not explicitly reported) with 63 lesions without IVUS assessments. No significant differences in postprocedure angiographic results were observed between the two groups: reference diameter (mm) ( $3.31 \pm 0.17$  [SD] vs.  $3.36 \pm 0.56$  [SD],  $p=0.69$ ); minimal luminal diameter (mm) ( $2.91 \pm 0.35$  [SD] vs.  $2.79 \pm 0.50$  [SD],  $p=0.23$ ); diameter stenosis (%) ( $12.6 \pm 8.3$  [SD] vs.  $16.5 \pm 10.5$  [SD],  $p=0.07$ ). In addition, no significant differences in these parameters were observed at short- (4 to 10 months) or long-term (5 to 9 years) followup. No clinical outcomes were reported.

Seo 1996 evaluated the use of IVUS after stent placement in 83 patients with angina and classified them into sufficient and insufficient dilatation groups defined as luminal area  $<5 \text{ mm}^2$  or luminal stenosis  $>60$  percent by IVUS, respectively. Patients in the insufficient dilatation group consequently received additional treatments, including larger balloon, longer dilatation time, DCA, or stenting (35 of 83 patients; 42%). The IVUS after stenting (83 patients) was compared with no IVUS after stenting (192 patients). The observed incidence of restenosis at 3 to 6 months of followup was 17 percent in the IVUS versus 42 percent in the no IVUS after stent placement, respectively (statistical significance not reported).<sup>58</sup>

**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?**

## Key Points

- There is insufficient evidence comparing different intravascular diagnostic techniques and their effects on outcomes
- Only one study rated as being at a high risk of bias provided relevant data for the comparison of FFR versus IVUS.

## Summary of Evidence

There is insufficient evidence regarding the comparison of FFR versus IVUS, as only one study rated as being at a high risk of bias provided relevant data. There is insufficient evidence



for all other comparisons, as none of the studies reviewed examining other intravascular diagnostic techniques addressed this Key Question.

## Available Evidence

One retrospective study rated as being at a high risk of bias due to the potential for selection bias and lack of adjusted analyses addressed this Key Question.<sup>59</sup> Nam 2010 compared the use of FFR-guided with IVUS-guided stent placement in patients with intermediate coronary lesions (40% to 70% diameter stenosis by visual assessment).<sup>59</sup> The study included 167 consecutive patients (83 in the FFR group and 94 in the IVUS group). The use of FFR or IVUS was based on operator preference. The cutoff value for the use of PCI in the FFR group was 0.80 and 4 mm<sup>2</sup> derived minimal lumen area in the IVUS group. Of 83 patients in the FFR group, 28 received stenting (34%), while 86 of 94 patients in the IVUS group received stenting (92%;  $p < 0.001$ ). The 1 year composite outcome of death/myocardial infarction/ischemia-driven target vessel revascularization was not significantly different between FFR and IVUS (3.6% vs. 3.2%;  $p = 1.00$ ). There were no significant differences between groups in postintervention MLD and percent diameter stenosis.

**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?**

## Key Points

- There is a moderate strength of evidence from one large sample size (9,070 patients) prospective study with a medium risk of bias that the effect of IVUS on outcomes did not vary by modifying factors including left main disease, sex, diabetes mellitus status, lesion length, and reference diameter.
- No studies addressed this Key Question for any technique other than IVUS.
- No studies addressed additional factors of interest, including chronic inflammation (e.g., systemic lupus erythematosus), and atherosclerosis following heart transplantation.

## Summary of Evidence

There is a moderate strength of evidence that the effect of IVUS on outcomes did not vary by factors such as left main disease, sex, diabetes mellitus status, lesion length, and reference diameter. There were no studies to address this Key Question for any technique other than IVUS.

## Available Evidence

Two studies, one multicenter prospective study (a post hoc RCT),<sup>41</sup> and one single center retrospective study<sup>47</sup> evaluated various factors that influenced the effect of IVUS-guided stenting on outcomes, compared with stent placement guided by angiography alone. The multicenter prospective study (a post hoc RCT), Orford 2004 was rated as being at a medium risk of bias due to potential for selection bias by excluding of subjects who refused to undergo followup

angiography. The single center retrospective study, Agostoni 2005 was rated as being at a high risk of bias due to the potential for selection bias and lack of adjusted analyses. Both studies enrolled CAD patients with angina, silent ischemia or patients with left main coronary artery disease who were undergoing a PCI procedure with or without stenting.

The multicenter prospective study (post hoc RCT) included 9,070 patients with an average age of 60 years.<sup>41</sup> The majority included were men (79%). The proportion of patients with diabetes was 24 percent, hypertension was 59 percent, and dyslipidemia was 67 percent. Smokers accounted for 24 percent, and the average ejection fraction was not reported in this study.<sup>47</sup> The average followup period was 9 months.<sup>41</sup>

The single center retrospective study included 58 patients with an average age 63 years.<sup>47</sup> The proportions of men included 68 percent. The proportions of patients with diabetes were 33 percent, hypertension was 59 percent, and dyslipidemia was 65 percent. Smokers accounted for 19 percent, and the average ejection fraction was 47 percent. The followup period for this study was 1 year.<sup>47</sup>

The multicenter prospective study (post hoc RCT), Orford 2004 evaluated various patient- and lesion-related factors—such as sex, diabetes mellitus status, lesion length, and reference vessel diameter—for their influence on the effect of IVUS-guided stent placement versus stenting guided by angiography alone, through interaction tests. These tests for interaction did not reach statistical significance for the composite clinical end point (any event), or any of their three individual components (death, myocardial infarction, or target-vessel revascularization;  $p>0.05$ ).<sup>41</sup>

The retrospective study, Agostoni 2005 stratified patients on the basis of left main disease (nondistal vs. distal) and evaluated the effect of IVUS-guided PCI among patients with different anatomic left main disease.<sup>47</sup> In multivariate analysis, patients with distal left main disease were significantly more likely to experience more adverse outcomes compared with those with nondistal left main disease (HR 7.7; 95% CI 1, 62.6,  $p=0.05$ ). The stratification on the basis of left main disease (nondistal vs. distal) revealed that IVUS-guided PCI was performed less often in patients with distal left main disease (31%, 10 of 32) than in patients with nondistal left main disease (54%, 14 of 26). However, regardless of the differences in anatomic left main disease, the rate of events was not significantly different between the IVUS-guided PCI group and the non-IVUS-guided PCI group.

Other than these two studies of IVUS, we found no studies of other intravascular diagnostic techniques that evaluated factors influencing the effect of intravascular diagnostic techniques compared with angiography alone or different intravascular diagnostic techniques on outcomes.

We found no studies evaluating additional subgroups of interest, including patients with and without diabetes, patients with chronic inflammation (e.g., systemic lupus erythematosus), and patients with atherosclerosis following heart transplantation.

# Discussion

## Key Findings and Strength of Evidence

Our review found that all the 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).

Our 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 and MI or of MACE in patients with intermediate coronary stenosis, as compared with stenting guided by angiography alone. Additionally, our review indicates that FFR-guided stenting would decrease costs of the procedure and would lead to fewer stents implanted, as compared with angiography alone. These findings 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 in order 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.

Based primarily on the FAME trial, 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.

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

The lower 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 their results may no longer be applicable to current clinical practice with a widespread use of drug-eluting stents.

In the reviewed studies, 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 risks of complications. Discussion regarding the report and recommendations for future research follow.

## Context of Findings

Our search identified three recently published systematic reviews comparing the effect of IVUS-guided PCI and non-IVUS-guided PCI. These reviews included a total of 21 nonoverlapping studies (9 trials in Casella 2003,<sup>15</sup> 15 in Berry 2000,<sup>60</sup> and 7 studies in Parise 2011<sup>61</sup>), with followup durations that ranged from 5 months to 2.5 years. Both randomized and nonrandomized trials, as well as registries, were included in these reviews. The clinical endpoints evaluated were target lesion revascularization, target vessel revascularization, MACE, mortality, MI, CABG, and restenosis. Angiographic outcomes including restenosis rate, MLD, percent diameter stenosis, acute gain, late lumen loss, net gain, and resource utilization were also evaluated. The definition of MACE varied across the reviews.

All three reviews consistently reported a significant reduction in 6-month angiographic restenosis rate and target vessel revascularization with IVUS-guided PCI versus non-IVUS-guided PCI. Two of these reviews also found a significant decrease in MACE with the use of IVUS for guiding PCI over non-IVUS-guided PCI.<sup>15,61</sup> No significant differences were observed between groups for the clinical outcomes of mortality or MI.

We reviewed 31 studies for comparisons of IVUS- and angiography-guided stent deployment, including two trials that were conducted in the era of drug-eluting stents. Our analyses revealed that only repeat revascularization was significantly lower in the IVUS-guided PCI group, as compared with the angiography-guided PCI group, during intermediate-term and long-term followup. Nonetheless, only six<sup>24,26,29,31-33</sup> and four<sup>23,25,27,30</sup> of the nine eligible RCTs had medium-term and long-term followup, respectively. Our review including recent literature did not find a significant decrease in MACE in the IVUS group compared with the angiography alone group. 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 found only two RCTs overlapping with our review, because of differences in eligibility criteria;<sup>15</sup> the second review searched until 2001 and identified only five of the total nine RCTs included in our review;<sup>60</sup> and the third review combined medium- and long-term data, found a statistically significant result for MACE.<sup>61</sup>

In this review, we examined both older studies (examining PCI with bare-metal stents) and more recent studies (examining PCI with drug-eluting stents). Our review also comprehensively evaluated nonrandomized comparative studies of intravascular diagnostic techniques. Our analyses evaluated both intermediate and clinical outcomes at various time points. Such extensive evaluations 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 on short-, intermediate-, and long-term outcomes, and found consistent results. In addition, our review synthesized data and analyzed gaps in the literature on the use of intravascular diagnostic techniques at various stages of the stenting (before, during, and after), and evaluated the role of these techniques in therapeutic decisionmaking. In summary, our review comprehensively examined both IVUS and FFR data, and has identified a lack of comparative studies for all other emerging novel and hybrid techniques.

## Applicability

Reviewed studies were all conducted in tertiary care centers (with only one exception<sup>37</sup>), and were carried out mostly in Western Europe and North America. Studies included patients with

various eligibility criteria for CAD undergoing PCI and stent placement at entry. Some studies included patients who had to be willing and be able to undergo followup angiography. 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<sup>62</sup>), thus limiting applicability in patients with severe CAD. Thus, overall, there are several important groups of patients who have not been adequately represented in the available studies.

Two studies reported the effect of various patient or lesion characteristics on outcomes among those who had an IVUS-guided stent placement versus stenting guided by angiography alone. These included controls of age, sex, and left main disease. These subgroup analyses were limited by a lack of reporting for all subgroups, or statistical analyses for other intravascular diagnostic techniques. Thus, no overall conclusion could be drawn regarding the effect of patient characteristics on outcomes for FFR-guided stent placement versus stenting guided by angiography alone.

Drug-eluting stent deployment came into clinical use since 2000. 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 (both conducted in Eastern Europe) 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.

## **Clinical and Policy Decisionmaking Implications**

There is moderate strength of evidence favoring FFR-guided PCI over angiography-guided PCI in patients with intermediate coronary lesions; these findings are supported by one large trial (FAME) 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.<sup>63</sup> Although some data exist for the role of FFR after intervention in side branches or after stent deployment, no randomized or direct comparative studies have evaluated FFR in these circumstances.<sup>64-66</sup> It is also worth noting that the FAME trial included patients with intermediate stenosis and lower grades of angina. The intrinsic risk of a non-ischemic 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, of course, 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. Additionally IVUS is used to assess stent apposition and adequate stent expansion, lesion coverage, and edge dissections when the operator is in doubt and 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). However, IVUS cannot fully assess the physiological significance of lesions (in deciding if a coronary lesion needs intervention), which depends not only on minimal lumen area, but also on numerous other factors including lesion length, reference vessel dimensions, and the amount of myocardium jeopardized by the lesion.

FFR and IVUS are often used as complementary modalities during an intervention to evaluate different aspects of coronary artery disease and decide its 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, and NIRS 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.

## **CER Limitations**

Intravascular diagnostic techniques are quickly evolving, which likely explains why we found few comparative studies except for two techniques, IVUS and FFR. There was insufficient evidence to answer two of the five review's Key Questions. Our review included only direct comparisons and only studies that had two distinct comparison groups (intravascular diagnostic technique and angiography vs. angiography alone). We excluded studies that lacked a distinct angiography-guided PCI group both at intervention and at followup. 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 time-frame 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).

## **Evidence Base Limitations**

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 MACE. Less than one-quarter of the included populations were women, and studies often did not evaluate the use of intravascular diagnostic techniques in patients with acute MI and left main disease. Most of the IVUS studies enrolled and followed patients before 2000. None of the studies included in our review was itself 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), owing to 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 the latest generation of stents. And studies often did not evaluate the effect of training of operators and their variability in the application of these techniques on clinical outcomes. Studies did not report on the effect of evolution intravascular diagnostic technique during study period.

## Ongoing Research

A search in the ClinicalTrials.gov registry yielded one active (recent, ongoing), one completed, and one recently terminated trial examining intravascular diagnostic techniques that are potentially relevant to the Key Questions in our report. None of the entries provided results. One RCT evaluated the effect of FFR-guided PCI. The remaining two RCTs compared IVUS-guided PCI with angiography-guided PCI.

The first RCT (DEFER-DES), conducted in South Korea, compared FFR-guided stenting with stent placement guided by angiography alone for the treatment of intermediate coronary lesions using drug-eluting stents, and has since been terminated owing to the slow enrollment (ClinicalTrials.gov number NCT00592228).

The second RCT (FAVOR) is an ongoing trial conducted in South Korea comparing the effectiveness of FFR-guided PCI with IVUS-guided PCI for the treatment of intermediate coronary lesions. The primary outcome of this trial is MACE; secondary outcomes are the individual components of MACE. Patients will be followed clinically for up to 2 years. This trial is expected to enroll 1,400 patients and will be completed by January 2014 (ClinicalTrials.gov number NCT01175863).

The third RCT (AVIO) is a completed study from Italy, comparing IVUS versus angiography alone in the optimization of drug-eluting stents (NCT00936169).

## Evidence Gaps

Table 2 summarizes the evidence gaps with regards to the five Key Questions of this systematic review.

**Table 2. Evidence gaps**

Key Question	PICO Categories	Evidence Gap
Key Question 1	Population	For the comparison between FFR-guided stenting or other intravascular diagnostic techniques and stenting guided by angiography alone:
		Because the vast majority of included studies enrolled a large proportion (>75%) of male patients with lower grades of angina, there is an evidence gap comparing the use of FFR-guided PCI with angiography-guided PCI in female patients and in patients with more serious diseases like left main disease or acute MI.
	Intervention	There is an overall evidence gap for this comparison because there were only 3 comparative studies on FFR.
	Comparator	There is an evidence gap comparing patients with low angina score who could be potentially eligible to receive aggressive medical therapy instead of PCI to patients who will receive stenting guided by FFR, angiography alone, or other intravascular diagnostic techniques.
	Outcome	There is an evidence gap for within 30 days outcomes because the single RCT only reported periprocedural MI, but did not provide data for in-hospital death, repeat revascularization, or MACE.
	General evidence gap	There is an overall evidence gap for this comparison because no studies compared the use of other intravascular diagnostic techniques besides FFR and angiography.

**Table 2. Evidence gaps (continued)**

Key Question	PICO Categories	Evidence Gap
Key Question 2	Population	For the comparison between IVUS guided stent placement and stenting guided by angiography alone:  The vast majority of included studies enrolled a large proportion (>75%) of male patients and all but one RCT specifically excluded patients with left main coronary artery disease or acute MI. Therefore, there is an evidence gap comparing the use of IVUS-guided stenting with angiography-guided stenting in patients with more serious diseases like left main coronary artery disease or acute MI.
	Intervention	There is lack of description of evolution of technology. Lack of IVUS trial data on the influence of operator's choice of balloon size and inflation pressures and their impact on clinical outcomes.
	Comparator	Because only two studies (both RCTs) conducted after year 2000 used the newer and current DESs, there is an evidence gap concerning the use of newer types of stents.
	Outcome	There is an evidence gap concerning long-term outcomes since neither RCT reported data on cardiac mortality and few studies reported outcomes greater than 1 year.
	General evidence gap	There is an overall evidence gap for this comparison because no studies compared the use of other intravascular diagnostic techniques besides IVUS and angiography.
Key Question 3	General evidence gap	There is an evidence gap because only two observational studies and with high risk of bias reported on this comparison.
Key Question 4	General evidence gap	There is an evidence gap because only one observational study and with high risk of bias reported on this comparison.
Key Question 5	General evidence gap	Other than for IVUS, no studies evaluated additional subgroups of interest, including patients with and without diabetes, patients with chronic inflammation (e.g., systemic lupus erythematosus), and patients with atherosclerosis following heart transplantation. There is an evidence gap in terms of lack of reporting of subgroup analyses of patients who underwent intravascular diagnostic-guided PCI compared with angiography-guided PCI and their impact on outcomes.

CABG = coronary artery bypass grafting; DES = drug-eluting stent ; FFR = fractional flow reserve; IVUS = intravascular ultrasound; MACE = major adverse cardiac event; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial

## Future Research Needs

This review has identified substantial gaps in the intravascular diagnostic technique literature. Chief among them are the contemporary role of IVUS guidance in the placement of drug-eluting stents; the prognostic role of FFR, which should be confirmed in further trials; and evaluation of hybrid and novel techniques for comparative efficacy and safety. While early studies evaluating drug-eluting stents have used IVUS during stent placement, comparative studies, particularly RCTs of drug eluting stent placement guided by IVUS or angiography alone, are lacking. The potential advantage of IVUS guidance in drug-eluting stent or bioabsorbable stent placement requires further evaluation. IVUS continues to be used in stenting 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 for other decisions 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) but otherwise would be treated with current best medical therapy only.<sup>12</sup> The role of FFR in high-risk patients with bifurcation lesions, left main coronary artery stenosis, ostial stenosis, acute coronary syndrome, or in side branches and other clinical situations, should be studied in future trials. The roles of FFR and IVUS in other vascular territories, outside of the coronary circulation, should also be better defined in future trials. Data correlating findings of high-resolution imaging techniques of OCT, IVUS-virtual histology, and NIRS with subsequent outcomes and events are not yet available. Although OCT is a very useful technology, particularly in stent research, its clinical role remains to be determined and will depend upon data demonstrating that OCT improves patient care and outcomes. The same applies for NIRS. Although the PROSPECT trial suggests that the addition of radiofrequency backscatter analysis to grayscale IVUS (IVUS-virtual histology) might provide incremental information in predicting the site of future coronary events, further studies are warranted to investigate this hypothesis, and at present, PCI of nonsignificant lesions on the basis of plaque composition alone is not justified.<sup>67,68</sup> 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 potentially add to the time, risk, and resource utilization of catheterization procedures.

At present, the lack of available comparative data for hybrid and novel devices (as opposed to individual 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 with computer analysis of coronary computed tomography angiograms or magnetic resonance angiograms.

Future research is also needed to enrich our understanding of the comparative effectiveness of angiography and intravascular diagnostic techniques (both older and novel) in diverse populations (including by race/ethnicity and socioeconomic status), in women, and in patients with left main disease and acute MI, as published studies often excluded or recruited a small proportion of these populations while evaluating established techniques such as FFR. 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 as compared with angiography.

Investigators should attempt to achieve consensus in harmonizing outcomes assessment. Studies either reported data by patients or by lesions, thereby 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 the use of FFR to decide whether intermediate coronary lesions require stenting confers a lower risk of death and MI, decreases procedural costs, 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<sup>21</sup>); 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 repeat revascularization 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 or bioabsorbable 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 coronary artery diseases. 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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## Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CABG	Coronary artery bypass graft surgery
CAD	Coronary artery disease
CER	Comparative Effectiveness Review
CFR	Coronary flow reserve
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
DCA	Directional coronary atherectomy
EPC	Evidence-based Practice Center
EQ-5D	European Quality of Life-5 Dimensions
FAME	Fractional Flow Reserve versus Angiography for Multivessel Evaluation (trial)
FDA	Food and Drug Administration (U.S.)
FFR	Fractional flow reserve
IMRI	Intravascular magnetic resonance imaging
IVUS	Intravascular ultrasound
MACE	Major adverse cardiac event
MLD	Minimal lumen diameter
MRI	Magnetic resonance imaging
MI	Myocardial infarction
NIRS	Near-infrared spectroscopy
NS	Not significant
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention
QCA	Quantitative coronary angiography
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
STEMI	ST-segment elevation myocardial infarction
TEP	Technical Expert Panel
TOO	Task Order Officer



## Appendix A. Search Strategy

Databases include: MEDLINE<sup>®</sup> and Cochrane Central Register of Controlled Trials

#	Searches
1	intravascular.af.
2	intra-vascular.af.
3	endovascular.af.
4	endo-vascular.af.
5	endocoronary.af.
6	endo-coronary.af.
7	intra-coronary.af.
8	intracoronary.af.
9	endoluminal.af.
10	endo-luminal.af.
11	transluminal.af.
12	trans-luminal.af.
13	intraluminal.af.
14	intra-luminal.af.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	magnetic resonance imaging.af.
17	magnetic resonance angiography.af.
18	exp magnetic resonance imaging/
19	exp magnetic resonance angiography/
20	elastography.af.
21	thermography.af.
22	microcirculatory resistance.af.
23	vascular resistance.af.
24	thermodilution.af.
25	exp Thermodilution/
26	hemodynamics.af.
27	exp Hemodynamics/
28	exp endosonography/
29	physiologic measurement*.af.
30	doppler ultrasound.af.
31	coronary pressure.af.
32	doppler velocimetry.af.
33	ultraso*.af.
34	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35	15 and 34
36	exp coronary angiography/
37	ultraso\$.af.
38	ffr.af.
39	fractional flow reserve.af.
40	coronary flow reserve.af.
41	coronary flow velocity reserve.af.
42	angioscop\$.af.
43	optical coherence tomography.af.
44	exp Tomography, Optical Coherence/
45	blood flow velocity.af.
46	exp Blood Flow Velocity/
47	doppler flow wire.af.
48	pressure wire.af.
49	coronary pressure measurement.af.
50	exp endosonography/
51	37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52	36 and 51
53	exp Ultrasonography, Interventional/
54	exp Fractional Flow Reserve, Myocardial/
55	fractional flow reserve.af.
56	intravascular ultrasound.af.
57	IVUS.af.
58	53 or 54 or 55 or 56 or 57
59	35 or 52 or 58
60	exp myocardial ischemia/
61	exp Angioplasty, Transluminal, Percutaneous Coronary/
62	exp stents/
63	exp Angioplasty, Balloon, Coronary/
64	exp Myocardial Revascularization/
65	exp drug-eluting stents/
66	61 or 62 or 63 or 64 or 65
67	60 and 66
68	59 and 67
69	remove duplicates from 68
70	exp animals/ not humans.sh.
71	69 not 70

## Appendix B. List of Excluded Studies

The 438 references (of the 519 total) that were excluded for reasons other than being a narrative review or case report are listed below.

Aarnoudse, W., Fearon, W. F., Manoharan, G., Geven, M., van, de, V, Rutten, M., De, Bruyne B., and Pijls, N. H. Epicardial stenosis severity does not affect minimal microcirculatory resistance. *Circulation*.110(15):2137-42. 10-12-2004.

UI - 15466646

Reject Reason: No direct comparison between techniques

Abaci, A., Oguzhan, A., Topsakal, R., Seyfeli, E., Yilmaz, Y., Eryol, N. K., Basar, E., and Ergin, A. Intracoronary electrocardiogram and angina pectoris during percutaneous coronary interventions as an assessment of myocardial viability: comparison with low-dose dobutamine echocardiography. *Catheterization & Cardiovascular Interventions*.60(4):469-76. 2003.

UI - 14624423

Reject Reason: No comparator of interest

Abizaid, A., Pichard, A. D., Mintz, G. S., Abizaid, A. S., Klutstein, M. W., Satler, L. F., Mehran, R., Leiboff, B., Kent, K. M., and Leon, M. B. Acute and long-term results of an intravascular ultrasound-guided percutaneous transluminal coronary angioplasty/provisional stent implantation strategy. *American Journal of Cardiology*.84(11):1298-303. 12-1-1999.

UI - 10614794

Reject Reason: No direct comparison between techniques

Abizaid, A., Albertal, M., Ormiston, J., Londero, H., Ruygrok, P., Seixas, A. C., Feres, F., Mattos, L. A., Staico, R., Silva, R. L., Webster, M., Stewart, J., Paoletti, F., Kataoka, T., Fitzgerald, P., Sousa, A., and Sousa, J. E. IMPACT Trial: angiographic and intravascular ultrasound observations of the first human experience with mycophenolic acid-eluting polymer stent system. *Catheterization & Cardiovascular Interventions*.66(4):491-5. 2005.

UI - 16283680

Reject Reason: No direct comparison between techniques

Agostoni, P., Vermeersch, P., Semeraro, O., Verheye, S., Van, Langenhove G., Van den,

Heuvel P., Convens, C., Van den, Branden F., and Bruining, N. Intravascular ultrasound comparison of sirolimus-eluting stent versus bare metal stent implantation in diseased saphenous vein grafts (from the RRISC [Reduction of Restenosis In Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent] trial). *American Journal of Cardiology*.100(1):52-8. 7-1-2007.

UI - 17599440

Reject Reason: Not relevant to KQs

Ahmed, J. M., Mintz, G. S., Waksman, R., Lansky, A. J., Mehran, R., Wu, H., Weissman, N. J., Pichard, A. D., Satler, L. F., Kent, K. M., and Leon, M. B. Serial intravascular ultrasound analysis of edge recurrence after intracoronary gamma radiation treatment of native artery in-stent restenosis lesions. *American Journal of Cardiology*.87(10):1145-9. 5-15-2001.

UI - 11356387

Reject Reason: No direct comparison between techniques

Al, Suwaidi J., Higano, S. T., Holmes, D. R., Jr., Rihal, C. S., and Lerman, A. Measuring maximal percent area stenosis poststent placement with intracoronary Doppler and the continuity equation and correlation with intracoronary ultrasound and angiography. *American Journal of Cardiology*.84(6):650-4. 9-15-1999.

UI - 10498133

Reject Reason: No outcome of interest

Albertal, M., Van, Langenhove G., Kay, I. P., Costa, M. A., Kozuma, K., and Serruys, P. W. Angiographic and clinical outcome of mild to moderate nonocclusive unstented coronary artery dissection and the influence on coronary flow velocity reserve. The Debate I Study Group. *American Journal of Cardiology*.86(4):375-8. 8-15-2000.

UI - 10946027

Reject Reason: No comparator of interest

Albertal, M., Van, Langenhove G., Regar, E., Kay, I. P., Foley, D., Sianos, G., Kozuma, K., Beijsterveldt, T., Carlier, S. G., Belardi, J. A., Boersma, E., Sousa, J. E., De, Bruyne B., Serruys, P. W., and DEBATE II Study Group. Uncomplicated moderate coronary artery

dissections after balloon angioplasty: good outcome without stenting. *Heart*.86(2):193-8. 2001.

UI - 11454840

Reject Reason: No direct comparison between techniques

Albiero, R., Hall, P., Itoh, A., Blengino, S., Nakamura, S., Martini, G., Ferraro, M., and Colombo, A. Results of a consecutive series of patients receiving only antiplatelet therapy after optimized stent implantation. Comparison of aspirin alone versus combined ticlopidine and aspirin therapy. *Circulation*.95(5):1145-56. 3-4-1997.

UI - 9054843

Reject Reason: No direct comparison between techniques

Alfonso, F., Macaya, C., Goicolea, J., Iniguez, A., Hernandez, R., Banuelos, C., Castillo, J. A., and Zarco, P. Angiographic changes induced by intracoronary ultrasound imaging before and after coronary angioplasty. *American Heart Journal*.125(3):877-80. 1993.

UI - 8438718

Reject Reason: Case report

Alfonso, F., Suarez, A., Angiolillo, D. J., Sabate, M., Escaned, J., Moreno, R., Hernandez, R., Banuelos, C., and Macaya, C. Findings of intravascular ultrasound during acute stent thrombosis. *Heart*.90(12):1455-9. 2004.

UI - 15547028

Reject Reason: No direct comparison between techniques

Alfonso, F., Garcia, P., Fleites, H., Pimentel, G., Sabate, M., Hernandez, R., Escaned, J., Banuelos, C., Perez-Vizcayno, M. J., Moreno, R., and Macaya, C. Repeat stenting for the prevention of the early lumen loss phenomenon in patients with in-stent restenosis. Angiographic and intravascular ultrasound findings of a randomized study. *American Heart Journal*.149(2):e1-8. 2005.

UI - 15846250

Reject Reason: No direct comparison between techniques

Algowhary, M., Matsumura, A., Hashimoto, Y., and Isobe, M. Poststenting axial redistribution of atherosclerotic plaque into the reference segments and lumen reduction at the stent edge: a volumetric intravascular ultrasound study. *International Heart Journal*.47(2):159-71. 2006.

UI - 16607044

Reject Reason: No direct comparison between techniques

Altstidl, R., Regenfus, M., Lehmkuhl, H., Dill, H., and Bachmann, K. Evaluation of successful PTCA by transstenotic flow velocity ratios. *Angiology*.48(9):775-82. 1997.

UI - 9313627

Reject Reason: No direct comparison between techniques

Andreini, D., Pontone, G., Bartorelli, A. L., Trabattoni, D., Mushtaq, S., Bertella, E., Annoni, A., Formenti, A., Cortinovis, S., Montorsi, P., Veglia, F., Ballerini, G., and Pepi, M. Comparison of feasibility and diagnostic accuracy of 64-slice multidetector computed tomographic coronary angiography versus invasive coronary angiography versus intravascular ultrasound for evaluation of in-stent restenosis. *American Journal of Cardiology*.103(10):1349-58. 5-15-2009.

UI - 19427427

Reject Reason: No direct comparison between techniques

Arakawa, K., Isoda, K., Sugiyabu, Y., Fukuda, M., Nishizawa, K., Shibuya, T., and Nakamura, H. Intimal proliferation after stenting reflected by increased stent-to-vessel cross-sectional area ratio: serial intravascular ultrasound study. *Journal of Cardiology*.32(6):379-89. 1998.

UI - 9914955

Reject Reason: No direct comparison between techniques

Athanasiadis, A., Haase, K. K., Wullen, B., Treusch, A. W., Mahrholdt, H., Voelker, W., Baumbach, A., Oberhoff, M., and Karsch, K. R. Lesion morphology assessed by pre-interventional intravascular ultrasound does not predict the incidence of severe coronary artery dissections. *European Heart Journal*. [6], 870-878. 1919.

UI - 9651710

Reject Reason: No direct comparison between techniques

az-Sandoval, L. J., Bouma, B. E., Tearney, G. J., and Jang, I. K. Optical coherence tomography as a tool for percutaneous coronary interventions. *Catheterization & Cardiovascular Interventions*.65(4):492-6. 2005.

UI - 15920721

Reject Reason: No direct comparison between techniques

Bach, R. G., Donohue, T. J., Caracciolo, E. A., Wolford, T., Aguirre, F. V., and Kern, M. J. Quantification of collateral blood flow during PTCA by intravascular Doppler. *European Heart Journal*.16 Suppl J:74-7. 1995.

UI - 8746942

Reject Reason: No direct comparison between techniques

Bachmann, R., Sechtem, U., Voth, E., Schroder, J., Hopp, H. W., and Schicha, H. Dipyridamole scintigraphy and intravascular ultrasound after successful coronary intervention. *Journal of Nuclear Medicine*.38(4):553-8. 1997.

UI - 9139119

Reject Reason: No outcome of interest

Bae, J. H., Kwon, T. G., Hyun, D. W., Rihal, C. S., and Lerman, A. Predictors of slow flow during primary percutaneous coronary intervention: an intravascular ultrasound-virtual histology study. *Heart*.94(12):1559-64. 2008.

UI - 18381376

Reject Reason: No outcome of interest

Balian, V., Galli, M., Repetto, S., Luvini, M., Galdangelo, F., Castiglioni, B., Boscarini, M., Petrucci, E., Filippini, G., and Marcassa, C. Intracoronary ST segment evolution during primary coronary stenting predicts infarct zone recovery. *Catheterization & Cardiovascular Interventions*.64(1):53-60. 2005.

UI - 15619303

Reject Reason: No IVDx technique used

Baptista, J., Di, Mario C., Ozaki, Y., Escaned, J., Gil, R., de, Feyter P., Roelandt, J. R., and Serruys, P. W. Impact of plaque morphology and composition on the mechanisms of lumen enlargement using intracoronary ultrasound and quantitative angiography after balloon angioplasty. *American Journal of Cardiology*.77(2):115-21. 1-15-1996.

UI - 8546076

Reject Reason: No direct comparison between techniques

Batkoff, B. W. and Linker, D. T. Safety of intracoronary ultrasound: data from a Multicenter European Registry. *Catheterization & Cardiovascular Diagnosis*.38(3):238-41. 1996.

UI - 8804778

Reject Reason: No comparison of interest

Bech, G. J., Pijls, N. H., De, Bruyne B., Peels, K. H., Michels, H. R., Bonnier, H. J., and Koolen, J. J. Usefulness of fractional flow reserve to predict clinical outcome after balloon angioplasty. *Circulation*.99(7):883-8. 2-23-1999.

UI - 10027810

Reject Reason: No comparison of interest

Bech, G. J., De, Bruyne B., Pijls, N. H., de Muinck, E. D., Hoorntje, J. C., Escaned, J., Stella, P. R., Boersma, E., Bartunek, J., Koolen, J. J., and Wijns, W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation*.103(24):2928-34. 2001.

UI - 11413082

Reject Reason: No direct comparison between techniques

Bech, G. J., Droste, H., Pijls, N. H., De, Bruyne B., Bonnier, J. J., Michels, H. R., Peels, K. H., and Koolen, J. J. Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. *Heart*.86(5):547-52. 2001.

UI - 11602550

Reject Reason: No direct comparison between techniques

Beleslin, B., Ostojic, M., Djordjevic-Dikic, A., Vukcevic, V., Stojkovic, S., Nedeljkovic, M., Stankovic, G., Orlic, D., Milic, N., Stepanovic, J., Giga, V., and Saponjski, J. The value of fractional and coronary flow reserve in predicting myocardial recovery in patients with previous myocardial infarction. *European Heart Journal*.29(21):2617-24. 2008.

UI - 18826987

Reject Reason: No direct comparison between techniques

Beleslin, B., Dobric, M., Sobic-Saranovic, D., Giga, V., Stepanovic, J., Djordjevic-Dikic, A., Nedeljkovic, M., Stojkovic, S., Vukcevic, V., Stankovic, G., Orlic, D., Petrasinovic, Z., Pavlovic, S., Obradovic, V., and Ostojic, M. Fractional flow reserve and myocardial viability as assessed by SPECT perfusion scintigraphy in patients with prior myocardial infarction. *Journal of Nuclear Cardiology*.17(5):817-24. 2010.

UI - 20524100

Reject Reason: No direct comparison between techniques

Bermejo, J., Botas, J., Garcia, E., Elizaga, J., Osende, J., Soriano, J., Abeytua, M., and Delcan,

J. L. Mechanisms of residual lumen stenosis after high-pressure stent implantation: a quantitative coronary angiography and intravascular ultrasound study.

Circulation.98(2):112-8. 7-14-1998.

UI - 9679716

Reject Reason: No comparison of interest

Bertrand, O. F., De Larochelliere, R., Joyal, M., Bonan, R., Mongrain, R., and Tardif, J. C.

Incidence of stent under-deployment as a cause of in-stent restenosis in long stents. The International Journal of Cardiovascular Imaging. [4], 279-284. 1920.

UI - 15529909

Reject Reason: No direct comparison between techniques

Bertrand, O. F., Poirier, P., Rodes-Cabau, J., Rinfret, S., Title, L., Dzavik, V., Natarajan, M., Angel, J., Batalla, N., Almeras, N., Costerousse, O., De Larochelliere, R., Roy, L., Despres, J. P., and VICTORY, trial investigators. A multicentre, randomized, double-blind placebo-controlled trial evaluating rosiglitazone for the prevention of atherosclerosis progression after coronary artery bypass graft surgery in patients with type 2 diabetes. Design and rationale of the VeIn-Coronary aTherOsclerosis and Rosiglitazone after bypass surgerY (VICTORY) trial. Canadian Journal of Cardiology.25(9):509-15. 2009.

UI - 19746240

Reject Reason: Measurement timepoint not of interest

Bertrand, O. F., Rodes-Cabau, J., Larose, E., Rinfret, S., Gaudreault, V., Proulx, G., Barbeau, G., Dery, J. P., Gleeton, O., Manh-Nguyen, C., Noel, B., Roy, L., Costerousse, O., De Larochelliere, R., and EARly Discharge after Transradial Stenting of CoronarY Arteries in Acute Myocardial Infarction (EASY-MI) Study Investigators. Intracoronary compared to intravenous Abciximab and high-dose bolus compared to standard dose in patients with ST-segment elevation myocardial infarction undergoing transradial primary percutaneous coronary intervention: a two-by-two factorial placebo-controlled randomized study. American Journal of Cardiology.105(11):1520-7. 6-1-2010. UI - 20494655

Reject Reason: No direct comparison between techniques

Blasini, R., Neumann, F. J., Richardt, G., Schmitt, C., Paloncy, R., and Schomig, A. Intravascular ultrasound-guided emergency coronary Palmaz-Schatz stent placement without post-procedural systemic anticoagulation. Heart.76(4):344-9. 1996.

UI - 8983682

Reject Reason: No direct comparison between techniques

Blasini, R., Neumann, F. J., Schmitt, C., Bokenkamp, J., and Schomig, A. Comparison of angiography and intravascular ultrasound for the assessment of lumen size after coronary stent placement: impact of dilation pressures. Catheterization & Cardiovascular Diagnosis.42(2):113-9. 1997.

UI - 9328688

Reject Reason: No direct comparison between techniques

Blessing, E., Hausmann, D., Sturm, M., Wolpers, H. G., Amende, I., and Mugge, A. Intravascular ultrasound and stent implantation: intraobserver and interobserver variability. American Heart Journal.137(2):368-71. 1999.

UI - 9924173

Reject Reason: No direct comparison between techniques

Blessing, E., Hausmann, D., Sturm, M., Wolpers, H. G., Amende, I., and Mugge, A. Incomplete expansion of Palmaz-Schatz stents despite high-pressure implantation technique: impact on target lesion revascularization. Cardiology.91(2):102-8. 1999.

UI - 10449881

Reject Reason: No direct comparison between techniques

Bodanese, L. C., Perin, E. C., and Gottschall, C. A. [Evaluation of post-intracoronary stent implant. Intravascular ultrasound versus quantitative angiography]. [Portuguese]. Arquivos Brasileiros de Cardiologia.64(5):439-46. 1995.

UI - 8526774

Reject Reason: No outcome of interest

Bonello, L., De Labriolle, A., Lemesle, G., Roy, P., Steinberg, D. H., Slottow, T. L., Xue, Z., Torguson, R., Kaneshige, K., Suddath, W. O., Satler, L. F., Kent, K. M., Lindsay, J., Pichard, A. D., and Waksman, R. Comparison of outcomes of drug-eluting stents versus bare-metal stents in nonostial proximal left anterior

descending coronary arteries. *American Journal of Cardiology*.103(4):496-500. 2-15-2009.  
UI - 19195509

Reject Reason: No direct comparison between techniques

Boschat, J., Matteodo, K., Gilard, M., Larlet, J. M., Provost, K., Jobic, Y., Guillo, P., Etienne, Y., Mansourati, J., and Blanc, J. J. [Endocoronary ultrasonography and quantitative coronary angiography. Correlations before and after transluminal coronary angioplasty]. [French]. *Archives des Maladies du Coeur et des Vaisseaux*.90(3):353-60. 1997.

UI - 9232073

Reject Reason: No outcome of interest

Boschat, J., Le, Breton H., Commeau, P., Huret, B., Bedossa, M., Gilard, M., and Stent Without BALloon Predilatation (SWIBAP) Study Group. Is coronary stent deployment and remodeling affected by predilatation? An intravascular ultrasound randomized study Stenting with or without predilatation: an IVUS study. *The International Journal of Cardiovascular Imaging*.18(6):399-404. 2002.

UI - 12537406

Reject Reason: No comparison of interest

Botas, J., Clark, D. A., Pinto, F., Chenzbraun, A., and Fischell, T. A. Balloon angioplasty results in increased segmental coronary distensibility: a likely mechanism of percutaneous transluminal coronary angioplasty. *Journal of the American College of Cardiology*.23(5):1043-52. 1994.

UI - 8144766

Reject Reason: Not relevant to KQs

Botman, C. J., Schonberger, J., Koolen, S., Penn, O., Botman, H., Dib, N., Eeckhout, E., and Pijls, N. Does stenosis severity of native vessels influence bypass graft patency? A prospective fractional flow reserve-guided study. *Annals of Thoracic Surgery*.83(6):2093-7. 2007.

UI - 17532405

Reject Reason: Not relevant to KQs

Bouma, B. E., Tearney, G. J., Yabushita, H., Shishkov, M., Kauffman, C. R., DeJoseph, Gauthier D., MacNeill, B. D., Houser, S. L., Aretz, H. T., Halpern, E. F., and Jang, I. K. Evaluation of intracoronary stenting by intravascular optical coherence tomography. *Heart*.89(3):317-20. 2003.

UI - 12591841

Reject Reason: No outcome of interest

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Reject Reason: No direct comparison between techniques

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UI - 15521203

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UI - 9704699

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UI - 17965485

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UI - 8141081

Reject Reason: No direct comparison between techniques

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Reject Reason: No outcome of interest

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Reject Reason: No comparator of interest

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UI - 15937934  
Reject Reason: Case report

Zimarino, M., Ausiello, A., Contegiacomo, G., Riccardi, I., Renda, G., Di, Iorio C., and De, Caterina R. Rapid decline of collateral circulation increases susceptibility to myocardial ischemia: the trade-off of successful

percutaneous recanalization of chronic total occlusions. Journal of the American College of Cardiology.48(1):59-65. 7-4-2006.

UI - 16814649

Reject Reason: No direct comparison between techniques

## Appendix C. Summary Tables

**Appendix C. Table 1. Study design and patient characteristics of FFR-guided stenting versus angiography-guided stenting (Key Question 1)**

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
Tonino 2009 Fearon, 2010 Pijls 2010 [19144937 21126973 20537493]	RCT Multicenter	2 yr	FFR	509	64.6 ± 10. 3	75.4	57.2	36.7	24.2	61.3	71.9	ND	ND	Low
US Europe FAME			Angio	496	64.2 ± 10. 2	72.6	57.1	36.3	25.2	65.9	73	ND	ND	
Wongpraparut 2005 [16188509] US	Prospective comparative Single center	2.5 yr	FFR	57	58 ± 10	75	52	ND	43	78	66	ND	ND	Medium non- randomized study; no matched or adjusted analysis
			Angio	80	62 ± 12	79	50	ND	34	70	60	ND	ND	



Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
Muramatsu, 2002 [12403892]	Prospective intervention with historical control	~2 yr	FFR	77	62 ± 11	79.3	ND	ND	12.5	ND	22.5	LAD 62.3 Multivesse I 48.1	ND	High historical control, intervention group prospective sample of consecutive patients; unadjusted analyses
Japan			Angio	77	64 ± 11	73.1	ND	ND	18.9	ND	24.3	LAD 39.7 Multivesse I 48.7	ND	

**Appendix C. Table 2. Study design and patient characteristics of IVUS-guided PCI versus angiography-guided PCI (Key Question 2)**

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
<b>RCTs</b>														
Frey 2000 [11076823] Germany The Strategy for IVUS guided PTCA and Stenting (SIPS) trial	RCT, 1 center	2 yr	IVUS	121	61.2 ± 8.1	82	ND	58	16	64	88	LAD 38 LCX 27 RCA 30 SVG 5	A 11 B1 37 B2 40 C 11	Medium, patient not blinded, no allocation concealment, "add on patients were rare" so randomization may have been violated
			Angio	148	60.7 ± 9.6	76	ND	52	16	56	87	LAD 41 LCX 27 RCA 30 SVG 3	A 15 B1 42 B2 34 C 8	
Gaster 2003 [12923023]	RCT, 1 center	2.5 yr	IVDx	54	57 (40-73)	100	ND	54	4	20	96	LAD: 30 LCX: 24 RCA: 28	A: 30 B1:24 B2: 28 C: 19	Medium, small sample size
			Angio	54	57 (33-78)	100	ND	44	11	24	93	LAD: 46 LCX: 26 RCA: 28	A: 24 B1:30 B2: 13 C: 33	
Gil 2007 [17892989] Poland Direct Stenting versus Optimal Angioplasty trial (DIPOL)	RCT*, 7 centers	0.5 yr (6 mo)	IVUS	83	56 ± 8	71	52 ± 9	44	10	ND	47	LAD: 34pt LCX: 22pt RCA: 27pt	A: 48 pt B1: 22 pt B2: 13 pt C: 0 pt	Medium, No blinding, no account for multicenter

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
			Angio	80	54 ± 8	73	48 ± 10	40	11	ND	40	LAD: 37pt LCX: 19pt RCA: 24pt	A: 49 pt B1: 21 pt B2: 10 pt C: 0 pt	
Jakabcin 2010 [19902491] Czech Republic HOME DES IVUS	RCT 1 center	1.5 yr (18 mo)	IVUS	105	59.4 ± 13	73	ND	37	42	67	63	LAD: 56 RCA: 29 RCX: 11 SVG: 1 Left main: 3	B2: 73 C: 27	Medium, no blinding, no allocation concealment
			Angio	105	60.2 ± 11	71	ND	32	45	71	66	LAD: 54 RCA: 24 RCX: 15 SVG: 3 Left main: 4	B2: 76 C: 24	
Kawata, 1997 9476578	RCT	ND	IVDx	17	64	82	ND	ND	18	35	ND	LAD 65 Cx 18 RCA 29	A 58 B 37 C 5	High, incomplete Design information. Analyses do not provide any variability measure
			Angio	25	60	48	ND	ND	36	36	ND	LAD 52 Cx 8 RCA 52	A 61 B 36 C 36	
Oemrawsingh 2003 [12515744] The Netherlands TULIP Study	RCT, 1 center	1 yr	IVUS	74	61 ± 10	95.9	0	ND	21.6	36.5	82.4	LAD 39 LCX 10 RCA 51	ND	Medium, patients not blinded

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
			Angio	76	63 ± 10	94.7	0	ND	27.6	39.5	81.6	LAD 38 LCX 21 RCA 41	ND	
Mudra 2001 [11560848] Germany OPTICUS	RCT, 26 centers	1 yr	IVUS	273	60.1 ± 10	77	56.5 ± 14	32	17	48	61	LAD: 51 LCX: 18 RCA: 30	A: 2 B1: 22 B2: 63 C: 13	Low
			Angio	275	61.5 ± 9.5	78	57.7 ± 14.3	32	17	52	67	LAD: 50 LCX: 14 RCA: 35	A: 3 B1: 20 B2: 62 C: 16	
Mueller 2002 [12362285] Switzerland A subset of SIPS	RCT, 1 center	2.3 yr (28 mo)	IVUS	19 (28 lesions)	65 ± 8	63	ND	63	100	63	84	LAD: 29 LCX: 29 RCA: 21 SVG: 0	B2: 32 C: 21	Medium
			Angio	24 (29 lesions)	63 ± 7	83	ND	67	100	67	88	LAD: 38 LCX: 41 RCA: 21 SVG: 21	B2: 55 C: 7	
Schiele 1998 [9708456] France RESIST	RCT, multi- center	0.5 yr (6 mo)	IVUS	79	57 ± 10	86	53 ± 13	68	11	30	68	LAD: 48 LCX: 11 RCA: 41	A: 6 B1: 51 B2: 34 C: 9	Medium, patients not blinded, randomization method not reported no allocation concealment
			Angio	76	56 ± 12	93	51 ± 9	63	11	34	68	LAD: 47 LCX: 11 RCA: 42	A: 11 B1: 41 B2: 34 C: 14	

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
Russo 2009 [20031704] US AVID	RCT	1 yr	IVUS	394	62 ± 12	73	53 ± 13	35	15	46	40	LAD: 40 LCX: 15 RCA: 35 SVG: 10 Left main 0.8:	ND	Low
			Angio	406	63 ± 11	68	55 ± 13	29	17	45	44	LAD: 37 LCX: 18 RCA: 32 SVG: 12 Left main: 0.5	ND	
<b>Nonrandomized comparative studies</b>														
Albiero 1997 [9386168] Italy, Germany	Matched cohorts, 2 centers	0.5 yr (6 mo)	IVUS	158 pt (173 lesions)	58.5 ± 8.9	90.5	ND	46.2	7.6	36.7	46.8	LAD: 61.3 LCX: 9.8 RCA: 27.7 Obtuse marginal branch: 1.2	A: 5.2 B1: 45.1 B2: 28.7 C: 11	Medium, observational, matched design
			Angio	154 pt (173 lesions)	58.1 ± 10	88.3	ND	42.5	6.5	55.6	80.9	LAD: 61.3 LCX: 9.8 RCA: 27.7 Obtuse marginal branch: 1.2	A: 10.4 B1: 33 B2: 43.9 C: 12.7	
Blasini 1998 [9716200] Germany	Prospective cohort 1 center	0.5 yr (6 mo)	IVUS	105	58.2 ± 10. 5	76.6	ND	35.2	16.2	52.4	38.1	LAD: 39.1 LCX: 17.2 RCA: 38.0 SVG: 5.7	A: 3.8 B1: 9.5 B2: 35.2 C: 48.6	Medium, observational study without adjustment

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
			Angio	107	59.9 ± 11.1	78.1	ND	37.4	14	49.5	32.7	LAD: 39.3 LCX: 15.8 RCA: 39.3 SVG: 5.6	A: 3.7 B1: 7.5 B2: 36.5 C: 52.3	
Choi 2001 [11431666] US	Retrospective study 1 center	0.5 yr (6 mo)	IVUS	100	60.4 +- 11.6	70	ND	50	26	67	65	LAD 49 LCX 23 RCA 27 L main 1	ND	Medium multivariate analysis was done in only 1 outcome (the composite outcome), retrospective design
			Angio	178	60.2 +- 11.5	73	ND	41	20	52	55	LAD 53 LCX 16 RCA 30 L main 1	ND	
Faulknier, 2004 [15156000] US	Retrospective comparativ e study 1 center	0.5 yr (6 mo)	IVUS	50 (70 lesio ns)	59.5 ± 11.5	74	ND	38	20	68	78	LAD 37 RCA 44 LCA 11 LMD 1.4 Vein graft 6	ND	retrospective, unclear selection of 50 of 173 IVUS guided PCI, matching by random number generator
			Angio	50 (65 lesio ns)	63.4 ± 12.1	66	ND	30	28	80	62	LAD 22 RCA 35 LCA 25 LMD 1.5 Vein graft 17	ND	

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
Orford 2004 [15389239] US, Canada, and other	A cohort of a RCT Multicenter worldwide	0.75 yr (9 mo)	IVDx	796	59.6 ± 10.2	79	ND	37	24	57	69	LMD 1 LCA 25 LAD 40 Right 34	A 12 B1 28 B2 44 C 16	Medium, post-hoc analyses of RCT, exclusion of patients who refuse angiographic follow-up, issue of selection bias in trial design.
			Angio	8274	60.3 ± 10.5	78	ND	37	23	60	64	LMD 1 LCA 24 LAD 41 Right 34	A 15 B1 30 B2 38 C 17	
Kim 2011 [21167352] Korea Korean Bifurcation Registry (COBIS)	Matched cohorts 16 centers	1.9 yr (23 mo) Max: 3 yr	IVDx	487	62 ± 9.6	66.5	60.1 ± 10.8	8.6	31.8	60	34.5	LAD: 83 LCX: 12.9 RCA: 4.1	ND	Medium, observational study without adjustment
			Angio	487	61.8 ± 10.2	66.9	58.8 ± 11	8	33.3	58.3	34.9	LAD: 82.5 LCX: 12.9 RCA: 4.5	ND	
Roy 2008 [18550555] US	Retrospective matched cohort, 1 center	1 yr	IVDx	884	66 ± 11.6	69.3	47 ± 15	43	35.9	81.8	86.2	LAD: 32.9 LCX: 24.7 RCA: 34.4 Left main coronary artery: 2 SVG: 5.8	A: 4.6 B: 73.1 C: 22.4 In-stent stenosis: 5.4	Medium, observational study with no adjustment, but with propensity score matching

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
			Angio	884	65.6 ± 11.8	70	48 ± 13	41.3	34.4	91.6	87.1	LAD: 33 LCX: 23.2 RCA: 34.3 Left main coronary artery: 2.3 SVG: 6.4	A: 5 B: 73.1 C: 21.9 In-stent stenosis: 4.3	
Sakamoto 1999 [10402282] Japan	Prospective cohort, 1 center	0.5 yr (6 mo)	IVDx	17 (18 lesions)	58 ± 7.5	82.4	ND	64.7	35.3	88.2	94.1	LAD: 55.6 LCX: 0 RCA: 44.4 Ostial: 11.1 SVG: 0	ND	Medium, small sample size, no adjusted analyses
			Angio	17 (19 lesions)	62 ± 7	76.5	ND	70.6	58.8	94.1	88.2	LAD: 63.2 LCX: 5.3 RCA: 31.6 Ostial: 15.8 SVG: 0	ND	
Park 2001 [11583882] Korea	Cohort, 1 center	2 yr	IVDx	77	54.7± 9.9	68	ND	ND	14	18	31	Os 52 Body: 17 Bifur:31	A 14 B1 34 B2 35 C 17	High, the use of IVUS was the operator's decision; selection bias could not be eliminated
			Angio	50	56.7± 10.9	70	ND	ND	18	20	28	Os 38 Body: 12 Bifur:50	A 10 B1 30 B2 40 C 20	



Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
Maluenda 2010 [19670305] US	Prospective cohort 1 center	1 yr	IVDx	382	63.6 ± 13. 3	66.2	43 ± 13	70.6	35.0	79.6	80.3	LAD: 41 LCA:24 RCA:27 LMCA:1 SVG:8	A: 4 B: 68 C: 28	High Baseline imbalance that were not properly accounted in multivariate analysis
			Angio	523	61.1 ± 14. 1	68.6	42 ± 11	85.3	24.9	73.6	76.1	LAD: 38 LCA:17 RCA:37 LMCA:0.4 SVG:7	A: 6 B: 62 C: 32	
Ozaki, 2007 [17186970] Japan REDUCE III	Prospective cohort 38 centers	0.6 yr (7 mo)	Total	521	66 ± 9	77	ND	31	30	57	45	ND	A 10 B1 27 B2 51 C 12	Medium unclear sampling, not adjusted for multiple comparisons
Faulknier 2004 [15156000] US	Retrospective cohort 1 center	0.5 yr (6 mo)	IVUS	50 (70 lesions)	59.5 ± 11.5	74	ND	38	20	68	78	LAD: 37 RCA: 44 LCA: 11 LMD: 1.4 Vein graft: 6	ND	High, retrospective, unclear selection of 50 of 173 IVUS guided PCI, matching by random number generator)
			Angio	50 (65 lesions)	63.4 ± 12.1	66	ND	30	28	80	62	LAD: 22 RCA: 35 LCA: 25 LMD: 1.5 Vein graft: 17	ND	

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
Yoshitomi 1999 [10385154] Japan	Cohort with historic controls, 1 center	0.25 yr (3 mo)	IVUS	38	63 ± 10	81.6	ND	53	21	53	26	LAD: 53 LCX:18 RCA: 30	A: 18 B1: 25 B2: 48 C:10	High, observational, with historical controls, with no confounder adjustment, small sample size
			Angio	28	64 ± 7	71.4	ND	68	21	50	25	LAD: 48 LCX: 17 RCA: 34	A: 14 B1: 24 B2: 52 C: 10	
Agostoni 2005 [15721110] The Netherlands	Retrospective cohort 1 center	1.2 yr	IVUS	24	62±1 2	62	52±10	37	37	58	62	ostial (29%) midshaft (29%), distal (42%)	ND	High The use of IVUS was the operator's decision; selection bias could not be eliminated
			Angio	34	64±1 3	73	44±14	50	29	59	68	ostial (9%) midshaft (26%), distal (25%)	ND	
Park 2009 [20031713] Korea	Registry 12 centers	3 yr	IVUS	756	59.7± 11. 5	69	62.7±8.5	7.4	27	48	30	ostium/sha ft 52 bifur 48	ND	Medium IVUS use was at the discretion of the operator; residual confounding could not be entirely eliminated by propensity score

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
MAIN- COMPARE			Angio	219	65.4± 11. 1	73	59.4±12. 2	7.3	33	55	27	ostium/sha ft 48 bifur 52	ND	
Talley, 1996 [8677866] US	Cross- sectional with comparator	NA	IVUS	23	54 ± 10	60	57 ± 10	48	52	ND	26	ND	ND	High unbalanced clinical characteristics ; no adjusted analysis
			Angio	37	52 ± 13	65	60 ± 9	22	11	ND	30	ND	ND	
Maluenda 2010 [19670305] US	Prospective cohort 1 center	1 yr	IVUS	382	63.6 ± 13. 3	66.2	43 ± 13	70.6	35.0	79.6	80.3	LAD: 40.7 LCX: 23.8 RCA: 26.7 SVG: 8 Left main: 0.6	A: 4.1 B: 67.8 C: 28.1	B/C Baseline imbalances not adjusted
			Angio	523	61.1 ± 14. 1	68.6	42 ± 11	85.3	24.9	73.6	76.1	LAD: 38.2 LCX: 17.8 RCA: 36.7 SVG: 6.5 Left main: 0.4	A: 5.5 B: 62.2 C: 32.3	
Fitzgerald 2000 [10920064] US CRUISE	RCT, 45 centers	0.75 yr (9 mo)	IVUS	270	60 ± 11	69	55 ± 10	32	23	52	39	LAD 46 LCX 18 RCA 36	A 8 B1 26 B2 57 C 9	Medium, no blinding, randomization method not reported
			Angio	229	61 ± 11	72	54 ± 12	41	18	59	33	LAD 43 LCX 24 RCA 33	A 10 B1 21 B2 60 C 9	

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
Claessen, 2011 [21939937] MATRIX	Registry, prospective cohort	2 yr	IVUS		64.3 ± 11.1	74.3	ND	29.9	30.1	81.2	84.5	LAD: 55.3 RCA: 26.1 LCX: 35.8 Left main: 4.8	B2/C: 68.2	Medium; authors attempted to adjust for confounding through propensity score matching
			Angio	1504	65.2 ± 11.1	74.7	ND	36.6	36.2	83.4	84.8	LAD: 36.8 RCA: 36.2 LCX: 35.2 Left main: 2.3	B2/C: 65.5	
Gerber 2009 19213067 Pravio study	Prospective study matched with an external cohort	30 days	IVUS	ND	ND	ND	ND	ND	9.7 (lesions)	ND	ND	ND	ND	Medium, only matched design analysis
			Angio	ND	ND	ND	ND	ND	9.7 (lesions)	ND	ND	ND	ND	
Fujimoto 2008 [18522771] Japan	Cohort, 1 center	0.6 yr (8 mo)	IVUS	132 (139 lesions)	65.3 ± 9.9	90.9	ND	ND	47.7	54.5	69.7	LAD: 33.8 LCX: 26.5 RCA: 35.6 Left main trunk: 2.9 SVG: 0	A 0 B1 33.1 B2 32.4 C 13.7	High, Little info on how IVUS was done; little info about recruitment and inclusion/exclusion criteria; unclear study design;

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
			Angio	327 (341 lesions)	66 ± 8.8	89	ND	ND	44.6	57.5	64.5	LAD: 38.1 LCX: 25.4 RCA: 31.2 Left main trunk: 0.9 SVG: 2.1	A 1.5 B1 29.6 B2 34.9 C 34	
Ahmed 2011 [21529735] S Korea KAMIR	Registry prospective cohort Multicenter	1 yr	IVUS	2127	61	76	54	ND	26	48	14	ND	C: 41; B: 39; A: 3	Medium; potential for confounding by indication
			Angio	8235	64	71	53	ND	27	50	12	ND	C: 38; B: 45; A: 4	
Biondi-Zoccai 2011 [21701872] Italy I-BIGIS	Registry prospective cohort Multicenter	2 yr	IVUS	226	65	83	55	41	23	63	63	ND	ND	Medium; potential for confounding by indication
			Angio	4088	65	81	55	32	26	67	58	ND	ND	
Youn, 2011 [22057856] S Korea	Registry data (nonrandomized comparative study) Single center	2 yr	IVUS	125	60 ± 12.9	74.4	45.1	9.6	27.2	50.4	22.4	ND	ND	Medium; potential for confounding by indication
			Angio	216	61.4 ± 11.6	63.0	48.0	6.0	32.9	51.4	11.1	ND	ND	

**Appendix C. Table 3. Study design and patient characteristics of IVUS-guided PCI versus angiography-guided PCI in evaluating success of stent implantation (Key Question 3)**

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
Nasu, 2004 [14996576] Japan	Retrospective comparative, 1 center	Shortterm 6 mo Longterm 5-9 yr	IVUS	Total 91 (101 lesions)	61±8	90	ND	66	36	64	76	Right 37 LAD 47 LCA 10 LMD 7	A/B1 37 B2/C 63	High selection bias, unadjusted analyses
Angio														
Seo 1996 [8934333] Japan	Retrospective comparative, 1 center	0.5 yr (3-6 mo)	IVUS	83	63	71	ND	28	ND	ND	ND	ND	LAD 54%; RCA 33%; LCX 13%	High Most validity items considered "N" or "ND"; possibility of introduction of major bias(es) that may affect the validity of the results cannot be ruled out.
Angio				192	ND	ND	ND	ND	ND	ND	ND	ND	ND	

**Appendix C. Table 4. Study design and patient characteristics of FFR-guided PCI versus IVUS-guided PCI (Key Question 4)**

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
Nam 2010 [20723852] Korea	Retrospective 1 center	1 yr	FFR	83	63	66	61	ND	22	42	16	proximal 48; mid 52	ND	High Unadjusted analysis; choice of therapy at operator's discretion; selection bias could not be eliminated
			IVUS	94	62	58	59	ND	26	51	15	proximal 46; mid 54	ND	

**Appendix C. Table 5. Study design and patient characteristics of IVUS-guided PCI versus angiography-guided PCI (Key Question 5)**

Author Year [UI] Country Study Name	Study Design, N Center	Followup Duration, yr	Interv Type	N	Age, yr	Male, %	Ejection Fraction, %	Previous MI, %	DM, %	HTN, %	Dyslipidemia, %	Stenoses Location, %	ACC/AHA Lesion Type, %	Risk of Bias Comments
Agostoni 2005 [15721110] The Netherlands	Retrospective cohort 1 center	1.2 yr	IVUS	24	62±12	62	52±10	37	37	58	62	ostial (29%) midshaft (29%), distal (42%)	ND	High The use of IVUS was the operator's decision; selection bias could not be eliminated
			Angio	34	64±13	73	44±14	50	29	59	68	ostial (9%) midshaft (26%), distal (25%)	ND	
Orford 2004 [15389239] US, Canada, and other	A cohort of a RCT Multicenter worldwide	0.75 yr (9 mo)	IVDx	796	59.6 ± 10.2	79	ND	37	24	57	69	LMD 1 LCA 25 LAD 40 Right 34	A 12 B1 28 B2 44 C 16	Medium, post-hoc analyses of RCT, exclusion of patients who refuse angiographic follow-up, issue of selection bias in trial design.
			Angio	8274	60.3 ± 10.5	78	ND	37	23	60	64	LMD 1 LCA 24 LAD 41 Right 34	A 15 B1 30 B2 38 C 17	

ND: no data, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, SVG: saphenous vein graft

NA: not applicable, ND: no data, MI: myocardial infarction, PCI: percutaneous intervention, MACE: major adverse cardiac events, TVR: target vessel revascularization, TLR: target lesion revascularization, IVUS: Intravascular ultrasound, QCA: Quantitative coronary angiography, Angio: angiography, FFR: fractional flow reserve, CFR: coronary flow reserve, RCT: randomized controlled trial, PTCA: percutaneous transluminal coronary angioplasty, CABG: coronary artery bypass graft, TIMI: thrombolysis in myocardial infarction,



DCA:directional coronary atherectomy, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, SVG: saphenous vein graft, DS-QCA:direct stenting technique guided with QCA, DS-IVUS:direct stenting guided with IVUS, POBA/IVUS:balloon angioplasty with IVUS guidance, POBA-FFR:balloon angioplasty guided with fractional flow reserve, MLD:minimal lumen diameter, MV:main vessel diameter, SB:side branch diameter, os:ostium, RVD:reference vessel diameter, RR:risk ratio, HR:hazard ratio, mo:months, AHA:American Heart Association, ACC:American Cardiology Association, EQ-5D scale:European Quality of Life-5 Dimensions scale, fu: followup, NRCS:nonrandomized comparative study, RD:risk difference

\*note, this study randomized patients into three groups: direct stenting with angio, direct stenting with IVUs, and balloon angioplasty with IVUS. For the current report, the group with balloon angioplasty is not relevant, and therefore not considered here.

**Appendix C. Table 6. Definition of MACE or composite outcomes among included studies**

<b>Author, Year</b>	<b>Outcome Name</b>	<b>Definition of Outcome</b>
<b>RCT</b>		
Frey 2000	MACE	Mortality, MI, repeat PCI, or CABG
Gaster 2003	Freedom from MACE	Freedom from mortality, Q wave MI, repeat PCI, and CABG
Gil 2007	MACE	Mortality MI, or RCR
Jakabcin 2010	MACE	Mortality, MI, or TLR
Mudra 2001	Composite outcome	Mortality, MI, CABG, or repeat PCI
Mueller 2002	Composite outcome	Mortality, non fatal MI, or TVR
Oemrawsingh 2003	Composite outcome	Mortality, MI, or TLR
Russo 2009	MACE	Any major adverse cardiac event
Schiele 1998	Composite	Mortality or TVR
<b>Nonrandomized studies</b>		
Agostoni 2005	MACE	Mortality, nonfatal MI, or TVR
Ahmed 2011	MACE	Mortality, nonfatal MI, and TVR
Biondi-Zoccai 2011	MACE	Mortality, MI or TLR
Choi 2001	MACE	Mortality, MI, repeat PCI, or CABG
Claessen 2011	MACE	cardiac death, MI or clinically driven TVR
Faulknier 2004	MACE	Mortality, MI, or TVR
Kim 2011	MACE	Mortality, MI, or TLR
Maluenda 2010	MACE	Mortality, Q wave MI, or TLR
Orford 2004	Composite outcome	Mortality, MI, or TVR
Park 2009	Composite outcome	Mortality or MI or TVR
Roy 2008	MACE	Mortality, Q wave MI, or TVR
Youn 2011	MACE	Mortality, MI, TVR, TLR

CABG: coronary artery bypass grafting; MACE: Major adverse cardiac events; MI: myocardial infarction; PCI: percutaneous coronary intervention; TLR: target lesion revascularization;TVR: target vessel revascularization;

**Appendix C. Table 7. Inclusion and exclusion criteria**

<b>Study</b>	<b>Recruitment Date</b>	<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
<b>FFR RCT</b>			
Tonino 2009		<ul style="list-style-type: none"> <li>• At least 2 <math>\geq 50\%</math> diameter stenoses <math>\geq 2</math> major epicardial vessels, both of which the investigator feels require stenting</li> <li>• Recent Non ST-segment elevation MI &lt; 5 days if the peak CK is &lt;1000 IU</li> <li>• Previous PCI</li> </ul>	<ul style="list-style-type: none"> <li>• Left main coronary disease</li> <li>• Previous coronary bypass surgery</li> <li>• Recent ST elevation MI (&lt;5 days)</li> <li>• Recent Non ST elevation MI (&lt;5 days) if the peak CK is &gt;1000 IU</li> <li>• Cardiogenic shock</li> <li>• Extremely tortuous or calcified coronary vessels</li> <li>• Life expectancy of &lt;2 y</li> <li>• Pregnancy</li> <li>• Contraindication for drug-eluting stent placement</li> </ul>
<b>FFR nonrandomized studies</b>			
Wongpraparut 2005	2000-2002	<ul style="list-style-type: none"> <li>• Stable angina and <math>\geq 2</math> single lesions located in different vessels</li> </ul>	<ul style="list-style-type: none"> <li>• Chest pain not responding to medical therapy</li> <li>• Previous coronary artery bypass grafting</li> <li>• Vessels that were totally occluded or supplying an akinetic territory by visual assessment of the left ventricular angiogram</li> <li>• Recent myocardial infarction</li> <li>• Ejection fraction &lt;50%.</li> </ul>
Muramatsu 2002	1997-1998	<ul style="list-style-type: none"> <li>• Consecutive patients admitted to a single hospital and diagnosed with first-time AMI</li> </ul>	<ul style="list-style-type: none"> <li>• Not reported</li> </ul>
<b>IVUS RCT</b>			
Mudra 2001	1994 - 1998	<ul style="list-style-type: none"> <li>• Angina or documented ischemia</li> <li>• No contraindication to antiplatelets therapy</li> <li>• Lesion length <math>\leq 25</math> mm to be covered with 1 or 2 stents in an artery with a diameter of <math>\geq 2.5</math> mm.</li> </ul>	<ul style="list-style-type: none"> <li>• Acute angina at rest</li> <li>• Complete akinesia in target artery supplied area</li> <li>• Significant left main lesion, bifurcation lesion, involvement of a side branch <math>\geq 2</math> mm in diameter with ostial stenosis.</li> </ul>

Russo 2009	1995 -1999	<ul style="list-style-type: none"> <li>• Patients over 18 years</li> <li>• Scheduled for elective coronary stent placement</li> </ul>	<ul style="list-style-type: none"> <li>• Dissection not covered by stent</li> <li>• Thrombolysis in myocardial infarction flow grade &lt;3 after stent placement</li> <li>• Chronic total occlusion, stent placement in a sole remaining circulation or left main equivalent</li> <li>• Stent placement within an aneurysmal portion of a vessel such that complete stent vessel wall contact could not be achieved</li> <li>• A bypass graft supplying a native vessel &lt;2.0 mm by visual estimate</li> <li>• Cardiac transplantation</li> <li>• Performance of IVUS during the index procedure before stent placement</li> </ul>
Schiele 1998	1995 - 1997	<ul style="list-style-type: none"> <li>• Symptomatic coronary artery disease with demonstrable ischemia</li> <li>• Single-vessel or native multivessel disease with &gt;70% stenosis of the target lesion, who had percutaneous transluminal coronary angioplasty followed by stent implantation for extensive dissection</li> <li>• Single &lt;20-mm long stent deployment</li> <li>• Optimal angiographic result after stent implantation, without dissection or residual stenosis &gt;20% as assessed visually or with on-line quantitative coronary angiography.</li> </ul>	<ul style="list-style-type: none"> <li>• Vessel diameter &lt;3.0 mm by visual estimation or on-line QCA</li> <li>• Coronary lesion &gt;15 mm in length</li> <li>• Previous bypass surgery</li> <li>• Contraindication to antiplatelet therapy (aspirin or ticlopidine)</li> <li>• Treatment of acute or chronic total occlusion,</li> <li>• Saphenous vein graft stenosis, recent (&lt;7 days) acute coronary syndromes</li> </ul>
Frey 2000	1996 - 1996	<ul style="list-style-type: none"> <li>• Patients undergoing elective or urgent PTCA or primary stenting in vessels of diameter 2.2 and 4.6 mm.</li> </ul>	<ul style="list-style-type: none"> <li>• Patients undergoing emergency intervention</li> <li>• Patients with planned atherectomy</li> <li>• Those with chronic total occlusion of the target vessel</li> </ul>
Oemrawsingh 2003	1998 - 2001	<ul style="list-style-type: none"> <li>• Patients having de novo, nonostial stenosis <math>\geq 20</math> mm length in a native coronary artery with a reference diameter that permitted implantation of <math>\geq 3</math>-mm stents without involvement of significant side branches (diameter <math>\geq 2.0</math> mm).</li> </ul>	<ul style="list-style-type: none"> <li>• Patients with recent (&lt;2 weeks) myocardial infarction (MI) or total occlusion</li> <li>• Those with contraindications for combined antiplatelet therapy with ticlopidine and acetylsalicylic acid</li> </ul>

Jakabcin 2011	2004 - 2005	<p>Patients fulfilling following criteria were included</p> <ul style="list-style-type: none"> <li>• Lesion type B2 and C according to the American Heart Association</li> <li>• Proximal left anterior descending artery</li> <li>• Left main disease</li> <li>• Reference vessel diameter &lt;2.5 mm</li> <li>• Lesion length &gt;20 mm</li> <li>• Instent restenosis</li> <li>• Insulin dependent diabetes mellitus</li> <li>• Acute coronary syndrome</li> </ul>	ND
Kawata 1997	ND	<ul style="list-style-type: none"> <li>• Patients with angina pectoris</li> <li>• Age 44 to 79 years</li> </ul>	<ul style="list-style-type: none"> <li>• Coronary artery diameter &lt;2.0 mm</li> <li>• Chronic total occlusion</li> </ul>
Mueller 2002	ND	<ul style="list-style-type: none"> <li>• Diabetic, consecutive patients</li> </ul>	ND
Gaster 2003	ND	<ul style="list-style-type: none"> <li>• Male</li> <li>• With stable angina pectoris</li> <li>• With de novo lesions in native coronary arteries, needed PCI</li> <li>• Patient of the Odense University Hospital</li> <li>• One or two coronary artery lesions by &gt; 50%.</li> </ul>	<ul style="list-style-type: none"> <li>• AMI &lt; 3 mo before scheduled PCI</li> <li>• Unstable angina within a month before the procedure</li> <li>• Left bundle branch block</li> <li>• Atrial fibrillation</li> <li>• Increased serum creatinine concentration (&gt; 200 mmol/l),</li> <li>• A total occlusion that could not be crossed with a guide wire</li> <li>• No IVUS pullback.</li> </ul>
Gill 2007	ND	<ul style="list-style-type: none"> <li>• Stable angina pectoris</li> <li>• Aged 18-70 years</li> <li>• 1 or 2 de novo vessel disease</li> <li>• Vessel reference diameter &gt;2.75mm</li> <li>• Lesion length up to 25mm.</li> </ul>	<ul style="list-style-type: none"> <li>• Recent myocardial infarction or unstable angina</li> <li>• Large calcifications seen on angiography</li> <li>• Large (&gt;2mm in diameter) side branch in segment to be stented</li> <li>• Chronic total occlusion</li> </ul>

Prospective	Cohort		
Blasini 1998	1994 - 1995	<ul style="list-style-type: none"> <li>• Patients with symptomatic ischemic heart disease in whom coronary stents were successfully placed after PTCA.</li> <li>• Patients with indications for stent placement as coronary artery dissections, complete vessel closure, and residual stenosis of 30% or more of the vessel diameter after PTCA.</li> </ul>	<ul style="list-style-type: none"> <li>• Patients with acute myocardial infarction</li> </ul>
Sakamoto 1999	1994 - 1997	<p>Consecutive patients with in-stent restenosis after prior Palmaz-Schatz stent identified by coronary angiography and underwent repeat PTCA. The first 20 consecutive patients were treated by balloon angioplasty without IVUS (22 lesions; quantitative coronary angiography [QCA] group). The subsequent 20 consecutive patients were treated by balloon angioplasty with IVUS (21 lesions; IVUS group).</p>	<ul style="list-style-type: none"> <li>• Patients with coronary occlusion due to acute or subacute coronary thrombosis with 1 mo after stent implantation</li> <li>• Patients with multiple stent implantation</li> </ul>
Fitzgerald 2000	1996 - 1997	<ul style="list-style-type: none"> <li>• Patients with symptomatic ischemic heart disease. <ul style="list-style-type: none"> <li>• Patients with new or restenotic lesions of the native coronary circulation.</li> <li>• Planned stent implantation with up to 2 stents deployed per patient.</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Patient requiring revascularization of lesions other than the stented lesion. <ul style="list-style-type: none"> <li>• Patients in whom use of aspirin, ticlopidine, or cumarin was contraindicated.</li> <li>• Patients with the presence of a left main coronary artery lesion.</li> <li>• Those having MI within the past 7 days.</li> <li>• Patients with occurrence of a stroke/transient ischemic neurological attack within the past 3 months.</li> </ul> </li> </ul>
Gerber 2009	2007 - 2008	<ul style="list-style-type: none"> <li>• Complex lesions. IVUS guided lesions were matched according to diabetes, vessel type, reference vessel diameter, minimum lumen diameter, and lesion length with a group of angio treated lesions. All IVUS optimized lesions matched 1:1 with angiographic optimized lesions from another institution. Matching was blinded to the final QCA results in both groups.</li> </ul>	<ul style="list-style-type: none"> <li>• No lesions were excluded.</li> </ul>

Ozaki 2007	ND	Included patients had: <ul style="list-style-type: none"> <li>• Unstable or stable angina,</li> <li>• A single target lesion in a native coronary artery with a vessel diameter &lt;4 mm</li> <li>• Planned stent implantation with up to 2 stents and agreement to follow-up angiography.</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindication to anticoagulation and antiplatelet therapy</li> <li>• Graft disease</li> <li>• Left main coronary artery disease.</li> </ul>
Orford 2004	ND	Patients undergoing stent implantation who consented for a follow-up angiography initially, followed by any patients without prerequisite for angio or IVUS. Some IVUS patients were enrolled at the discretion of operator.	Initial exclusion who did not undergo followup angiography.
<b>Retrospective</b>	<b>Cohort</b>		
Albiero 1997	1993 - 1995	Had angiographic followup with a QCA. Matched IVUS group (in Italy) with angio only group (in germany). For the IVUS group, IVUS cannot be used before stenting. Matching was based on (1) sex, (2) history of diabetes, (3) previous PTCA at the same site, (4) vessel treated, (5) reference diameter $\pm 0.3$ mm, (6) baseline MLD $\pm 0.1$ mm, and (7) number $\pm 0.5$ of stents deployed.	ND
Yoshitomi 1999	1996 - 1997	<ul style="list-style-type: none"> <li>• Stable angina pectoris or previous MI or acute MI. Two groups were patients of different time periods. Like historical controls.</li> </ul>	<ul style="list-style-type: none"> <li>• Chronic total coronary artery occlusion.</li> </ul>
Choi 2001	1997 - 1998	<ul style="list-style-type: none"> <li>• Patients with symptomatic coronary artery disease who underwent elective and emergency coronary artery stenting of a single native coronary vessel.</li> </ul>	<ul style="list-style-type: none"> <li>• Patients receiving stent implantations of saphenous vein grafts or multiple vessels</li> </ul>
Faulknier 2004	2001	<ul style="list-style-type: none"> <li>• Randomly selected cases undergone PCI in a single community hospital center.</li> </ul>	ND
Agostoni 2005	2002 - 2003	<ul style="list-style-type: none"> <li>• Unprotected left main disease for elective drug eluting stent</li> </ul>	<ul style="list-style-type: none"> <li>• Acute MI or cardiogenic shock undergoing emergency PCI or LMCA CABG</li> </ul>
Fujimoto 2008	2004 - 2006	<ul style="list-style-type: none"> <li>• Patients who had sirolimus-eluting stent implantation</li> </ul>	ND
Park 2001	ND	<ul style="list-style-type: none"> <li>• Symptomatic LMCA disease, OR</li> <li>• Documented myocardial ischemia and angiographic <math>\geq 50\%</math> diameter stenosis.</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindication to antiplatelets or anticoagulation therapy</li> <li>• LVEF &lt;40%.</li> </ul>

Youn 2011	2003-2008	•Patients with ST-elevated myocardial infarction (STEMI)	•Patients who died first hospitalization
Nasu 2004	1992-1997	• Patients who had undergone successful stand-alone directional coronary atherectomy and had short-term follow-up angiography	• Patients who had died, or had any target vessel revascularization
Seo 1996	1992-1994	•Patients with angina pectoris who had undergone percutaneous coronary angioplasty	• Diameter of the distal coronary artery 1.5 mm or less and impossible to advance the IVUS catheter; possibility of ischemia due to a catheter insertion
<b>Registry</b>			
Ahmed 2011	2006-2010	•Patients with AMI and had PCI	• Cardiogenic shock, rescue PCI after IV thrombolysis
Biondi-Zoccai 2011	2002-2006	• Consecutive patients undergoing PCI at a bifurcation lesion of a major epicardial vessel	No specific exclusion criteria
Claessen 2011	2004-2006	• Diagnosed with single- or multivessel coronary artery disease, undergoing PCI with at least 1 stent placement, de novo or restenotic (including in-stent restenosis and coronary brachytherapy failure) lesions needing stent	• Allergic to aspirin, clopidogrel or ticlopidine, heparin, bivalirudin
Park 2009	2000 - 2006	• Elective PCI for unprotected LMCA stenosis	• Prior CABG • Concomitant valvular or aortic surgery, presented with cardiogenic shock or MI.
Roy 2008	2003 - 2006	Registry of consecutive patients in Washington Hospital Center had drug-eluting stents (DES) implantation. Sample of patients with IVUS and a sample of propensity score-matched patients with angiographic guidance only were analyzed. Score was matched for clinical and angiographic characteristics.	ND
Maluenda 2011	2003 - 2007	• Patients surviving the hospitalization	• Patients with cardiogenic shock and rescue PCI after intravenous thrombolysis



Kim 2011	2004 - 2006	<ul style="list-style-type: none"> <li>• Main vessel (MV) diameter <math>\geq 2.5</math> mm and side branch (SB) diameter <math>\geq 2.0</math> mm</li> <li>• Sample of patients with IVUS guidance and a sample of propensity score-matched patients with angiographic guidance were analyzed.</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiogenic shock</li> <li>• ST-segment elevation acute myocardial infarction within the previous 48 hours</li> <li>• Life expectancy <math>&lt; 1</math> yr</li> <li>• Left main bifurcation</li> </ul>
<b>Cross-Sectional</b>			
Talley 1996	ND	<ul style="list-style-type: none"> <li>• Patients going through elective standard balloon angioplasty.</li> </ul> <p>Note: group assignment was based on patients' clinical characteristics.</p>	<ul style="list-style-type: none"> <li>• Multiple vessel coronary angioplasty</li> </ul>
<b>FFR Versus IVUS</b>			
Nam 2010	2006-2008	<ul style="list-style-type: none"> <li>• 40-70% stenosis by visual impairment; single lesion in the proximal/mid part of a major epicardial artery with reference vessel diameter <math>&gt; 2.5</math> mm; no documented evidence of ischemia</li> </ul>	<ul style="list-style-type: none"> <li>• Had primary or emergent PCI for ACS; had CABG; multiple lesions in the same artery; left main disease, primary myocardial disease, or a major life threatening illness; contraindications to adenosine, ASA or clopidogrel</li> </ul>

## Appendix D. Description of Intravascular Diagnostic Techniques

Intravascular diagnostic Techniques	Device Names	Manufacturers	FDA Clearance	Date of FDA Clearance
Fractional Flow Reserve (FFR)	PressureWire™ Aeris Wireless FFR Measurement System	St. Jude Medical	Yes	April 24 1998
	PressureWire® Certus with RADIAnalyzer® Xpress monitor	St. Jude Medical	Yes	July 1 2008 (Pressure wire) Oct 9 2009 (RadiAnalyzer Xpress)
	Horizon Cardiology™	McKesson	Yes	Nov 8 2006
	OptoWire	Opsens Inc.	No	
	ComboMap® Pressure and Flow System	Volcano Corporation	Yes	June 2 2004
Coronary Flow Reserve (CFR)	FloWire® Doppler Guide Wire	Volcano Corporation	Yes	Nov 24 2004
Intravascular Ultrasound (IVUS)	Volcano s5i™ Imaging System	Volcano Corporation	Yes	Oct 8 2008
	iCross™ Coronary Imaging Catheter	Boston Scientific	No (Recalled on March 28 2011)	
Intravascular Ultrasound (VH-IVUS) with Virtual Histology	VH® IVUS Imaging System	Volcano Corporation	Yes	Aug 18 2005
	Volcano imaging system with a 20-MHz Eagle Eye Gold IVUS imaging catheter	Volcano Therapeutics Inc, Rancho Cordova, Calif	Yes	Aug 18 2005
Optical Coherent Tomography (OCT)	C7-XR™ OCT Intravascular Imaging System	LightLab Imaging Inc./ St. Jude Medical	Yes	Apr 30 2010

	C7 Dragonfly™ Intravascular Imaging Catheter	St. Jude medical	Yes	Apr 30 2010
<b>Near-Infrared Spectroscopy (NIR)</b>	LipiScan	<b>InfraReDx, Inc</b>	Yes	April 25 2008
	NIR spectrometer model 6500	FOSS NIRSystems, Inc.	No	
<b>Angioscopy</b>	A5000	Applied Medical Resources Corporation	Yes	July 11 1995
<b>Intravascular Magnetic Resonance Imaging (MRI)</b>	Cathamaran™ IVMRI System	TopSpin Medical Inc.	No	
<b>Elastrography</b>	Galaxy IVUS scanners	Boston Scientific	Yes	April 22 1998
	LOGIQ E9 ultrasound platform	GE Healthcare	Yes	August 15 2008
	Atlantis® SR Pro Imaging Catheter	Boston Scientific	Yes	Nov 30 2006
<b>Thermography</b>	Epiphany Coronary Thermography Catheters	Rontis	No	