Comparative Effectiveness Research Review Disposition of Comments Report

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

Draft review available for public comment from May 17, 2012 to June 14, 2012.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	General Comments	Quality of the Report: Superior This is a well written systematic review evaluating the comparative effectiveness of intravascular diagnostic techniques addition to angiography compared to angiography alone in patients with CAD undergoing PCI with stent deployment. This is an important report clinically since there are many intravascular diagnostic techniques available, and the use of these new technologies in addition to traditional coronary angiography is variable dependent on institution, referring physician and operator. This review helps to identify the strength of data in support of usage of these additional intravascular diagnostic techniques, in which clinical situations each technique is the most useful, and the effect on treatment decisions and overall outcomes. Although not explicit in the title, the target populations focused on this review are patients with CAD diagnosed on angiography, who are expected to undergo PCI with stenting. The key questions are appropriate to this specific population and are clearly stated. Another population that is not addressed in this review but is of additional interest, are patients with signs and symptoms of CAD, but no evidence of CAD on coronary angiography. The use of intravascular diagnostic techniques addressed in this review in addition to angiography may identify patients with CAD or microvascular disease who may benefit from disease specific therapies, but who may be underdiagnosed with standard coronary angiography.	Thank you. We have added “coronary artery stenting” to the title. The specific populations without CAD but are undergoing angiography were not part of the Key Questions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	General Comments	Quality of the Report: Good I found the review to be thorough and well written. I do feel that it misses some of the very difficult CASE SPECIFIC issues an interventional cardiologist may face that cannot be pigeon holed into an evidence based guideline	Thank you. Some difficult case-specific issues that are faced in routine clinical practice can be underrepresented in the literature, and therefore require careful deliberation between patients and their interventional cardiologists. This report is an evidence-based review. We do not make clinical practice recommendations, and this review should not be mistaken for a Clinical Practice Guideline document. Discussions and assessment of case-specific issues are very important for the clinicians and cannot be fully addressed by systematic reviews alone. Such case-specific issues are best handled by decision-analytical frameworks. We do hope that the future CER reports will incorporate such decision-analytical frameworks to guide clinicians on very difficult case-specific issues.
Peer Reviewer 4	General Comments	New evidence should upgrade recommendations from moderate to high but not affect the direction of the effect. Quality of the Report: Good This impressive review is an excellent summary of the impact of FFR and IVUS on clinical outcomes related to PCI. The real challenge is that on 1 hand the evidence is old and on the other, new and emerging data is yet to be published. As a result, practice has already changed despite the evidence cited.	We have retained the summary of evidence as being “moderate” because the new evidence (the FAME II trial) was not eligible according to our criteria. 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. Thank you. We acknowledge that the practice patterns have changed and progressed well ahead of the available evidence cited.
Peer Reviewer 5	General Comments	Quality of the Report: Superior This is a clinically meaningful study. The weight of evidence suggests that the use of FFR reduced the rate of target lesion revascularization, but not MI or death. In this respect further studies are needed to determine the value of FFR for a decision-making. On the other hand the value of IVUS for optimization of stenting in the era of drug-eluting stenting has not been investigated in randomized trials. The above questions are explicitly addressed.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	General Comments	This is a well written report and have pointed out the knowledge gap that exists between the application of FFR/IVUS and clinical outcomes in patients with coronary artery stenosis. The authors have explicitly presented the main points and limitations of the FFR/IVUS. The above report is worthy of publication to elucidate the needs for future randomized trials.	Thank you.
Peer Reviewer 6	General Comments	Quality of the Report: Good Nicely performed review of available evidence supporting adjunctive modalities within the cath lab for use in patients with coronary artery disease	Thank you.
Peer Reviewer 7	General Comments	Quality of the Report: Good In general, the authors should be commended on a very nice review of the literature surrounding the use of intravascular diagnostic techniques for the evaluation of coronary lesions. The authors have clearly defined 5 relevant, key questions, and the literature review for these questions is complete. The authors have neglected to cite two of the most heavily cited studies in this field, however: the DEFER Trial (J Am Coll Cardiol 2007;49:2105–11) and FAME 2. While DEFER and FAME 2 do not fit within the context of the 5 key questions, they are two of three randomized studies (with FAME) that have now established the utility of FFR in the evaluation of intermediate coronary lesions. Both DEFER and FAME 2 randomized patients to optimal medical therapy + PCI versus OMT alone. DEFER demonstrated no benefit to OMT+PCI in patients with an FFR>0.8 while FAME 2 demonstrated a benefit among those with an FFR<0.8. Any review of the utility of FFR should include some mention of these two studies.	Thank you. We have added that these two trials did not meet the eligibility criteria 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.
Peer Reviewer 1	Introduction	The introduction is well written and clearly states the burden of disease, the proposed advantages with use of intravascular diagnostic techniques, and the current uncertainties with their use. There is a good summary of different types of intravascular diagnostic techniques currently in use either clinically or for research including the current reimbursement status for each technique. The key questions are again clearly summarized.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	Introduction	Preface and Structured Abstract well done but again do not emphasize the limitations that are inherent in a guideline for procedures that have so many variables that may unfold during a case. “TVR” is used without any definition.	This report is an evidence-based review and is not a Clinical Practice Guideline document. There are many scenarios that did not fall within the scope of an evidence review. Such clinical scenarios will probably require careful deliberation between patients and their interventional cardiologists. Future CER reports will need to incorporate such decision-analytical frameworks to guide clinicians on very difficult case-specific issues. We have changed TVR to repeat revascularization, as all or most of the studies have defined it as clinically-driven repeat revascularizations.
Peer Reviewer 4	Introduction	Excellent summary	Thank you.
Peer Reviewer 5	Introduction	FFR does have moderate strength for the assessment of intermediate lesions. FAME study did not include high-risk patients such as those with bifurcation lesions or the left main coronary stenosis. The value of IVUS for assessment of an intermediate lesion is limited and should not be used for a decision making strategy. There is a paucity evidence that the use of IVUS would improve the outcome of patients after stenting in the era of drug eluting stents.	These considerations have been added to our discussion section. We evaluated IVUS data for decisionmaking when available. The paucity of evidence regarding the use of IVUS in drug eluting and newer stents is already stated in the report.
Peer Reviewer 6	Introduction	Page 10, line12: “Revascularization is the standard treatment for CAD” -- this summary is not true in all contexts. It would be better to rephrase this as revascularization is a commonly accepted treatment for patient’s with CAD	We have revised this sentence as per your suggestion.
Peer Reviewer 6	Introduction	Page 10 line 34: “Whether a stent was successfully placed”– she better be stated as it is difficult to determine whether a stent was fully expanded and apposed to the intraluminal border by angiography alone	We have revised this sentence as per your suggestion.
Peer Reviewer 6	Introduction	Page 10 line 58: “Before the plaques have attained a maximum maturity”–I believe you’re trying to say before plaques have a chance to potentially rupture and cause a potential myocardial infarction. This is different than the concept of maturity.	We have revised this sentence as per your suggestion.
Peer Reviewer 7	Introduction	No comments. This is appropriate.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Methods	The inclusion criteria are very broad and appropriate given the current literature on this topic. Both randomized and non-randomized comparative studies were included. The search strategies used appear appropriate and logical. The full search terms and combinations used are included in the appendix. Comparators used for each of the Key Questions are clearly defined, and the outcomes of interest including definitional time points appear to be clearly defined. Statistical tests for the meta-analyses appear appropriate using a random effects model of DerSimonian and Laird, with inclusions of a estimate of statistical heterogeneity and sensitivity analyses.	Thank you.
Peer Reviewer 3	Methods	The Methods seem fine. However, their needs to be attention paid to the specific issues pertaining to coronary artery bypass grafts (interesting study in Am J Cardiology 2012;109:1576-1581). I agree that because of the limitations in the available studies gender differences could not be addressed but what about looking at possible issues relating to size (body surface area) and age? Utility of IVUS for commonly used indications such as stent thrombosis to check for stent underexpansion should be considered.	We have included all specific applications of IVUS, from the studies comparing IVUS with angiography alone. We have evaluated study-level subgroup data if available in primary studies. We did not find subgroups relevant to age or body surface area. When available, we have reported these under stent-related outcomes.
Peer Reviewer 4	Methods	Methods are robust, populations inclusive of the evidence at hand and the statistical methods are sound.	Thank you.
Peer Reviewer 5	Methods	Given the limitation of the study, it seems that inclusion and exclusion of the study is reasonable. The research strategies are clearly stated. The outcome measures are appropriate. The statistical methods are sound.	Thank you.
Peer Reviewer 6	Methods	Methodology for review appeared sound. No specific comments	Thank you.
Peer Reviewer 7	Methods	The methods are appropriate, and there is an appropriate reference to the timing of these studies in the limitations section. I would agree that the relevance of older IVUS data is unclear in today's practice.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Results	The results for each of the key questions are nicely presented in the key points with adequate descriptions of each of the studies used in the analyses. There are a few inconsistencies noted. 1. Results are reported in similar fashion across most of the results, but in Key Question 2, Intermediate Outcomes under Resource Utilization, the first sentence should perhaps be reworded to state that there were 4 RCTs that evaluated used of glycoprotein IIb/IIIa inhibitor in IVUS-guided PCI group (page 25, lines 14-15). The assumption is that none of the non-randomized studies reported this outcome since only RCT's are listed.	We have edited this sentence. Resource utilization includes many different outcomes, including the use of glycoprotein IIb/IIIa inhibitor, procedural time, the use of contrast medium, fluoroscopy time, and the utilization of other resources.
Peer Reviewer 1	Results	2. Also, in QCA Process Outcomes, the data on MLD measurements there seems to be some discrepancy in the number of studies reported in the text (9 RCTs and 6 non-randomized studies for data reported by patient) with Figures 3 and 4 which for patient level data are shown for 6 RCT's and 6 non-randomized studies (Ozaki with 2 reports).	These results have been updated to incorporate newly published data. We have added footnotes to clarify the results in the table (e.g., when more than two data points came from the same study).
Peer Reviewer 1	Results	3. Figure 8 reference in the text appears on page 26, line 56 appears to refer to Figure 5 Forest plot on page 27, and Figure 5 reference in the text on page 27, lines 54-55 appears to refer to Figure 7 on page 28.	Thank you. We have revised these sections.
Peer Reviewer 1	Results	4. The change in the plot coordinates (Favors Angiography-guided versus Favors IVUS-guided) seems to change from figure to figure, but would be easier to follow if consistent from figure to figure (i.e. Favors angiography-guided always to the left or always to the right of the center point).	We have modified these figures and added an arrow to show the direction of benefit so that readers will not be confused about the flipping of "favors IVUS". The flipping occurs because some outcomes are beneficial outcomes and some are not. We have provided explanations below the plots in question.
Peer Reviewer 1	Results	5. The last sentence on page 28 going onto page 29 as written seems to suggest that there is only 1 study that analyzed data on medium term percent diameter stenosis by patient level. However, there was only 1 non-randomized study that favored IVUS guided, but there were also 4 RCT's that analyzed on patient level and meta-analysis of this data was not-significant.	We've edited this sentence for clarity.
Peer Reviewer 1	Results	6. Similar to point 4, when forest plots of RCT and Observational studies are presented together, would be easier to follow if there is consistency in the reported data (i.e. RCT data always demonstrated above the Observational data).	We have revised per your suggestion.
Peer Reviewer 3	Results	See above and below. Overall presentation looks good	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Results	An important issue arising from this data deals with operator-related outcomes. The clinical outcomes can be quite divergent and the review should address or at least question practice-related factors. FFR appears much more likely to be adopted widely than IVUS, which is highly dependent on the operator.	We did not review evidence regarding operator-related outcomes or diffusion of technology.
Peer Reviewer 5	Results	The study is detailed and appropriate. The characteristics of the study are clearly stated. The key messages are explicit. There are too many appendices. They can be shortened. The authors included the studies appropriately.	Per your suggestion, we have shortened the appendices.
Peer Reviewer 6	Results	Multiple times within the document, as in page 16 line 28, the term intermediate coronary lesion and greater than equal to 50% stenosis are combined. From a clinical angiographic standpoint, it is commonly accepted that and intermediate coronary stenosis is 40-70% angiographically narrowed. There may be some confusion with respect to 50% level as that was the cut off used for the FAME trial. It must be remembered that the FAME trial utilized this cut off because stenting of lesions less than 50% without other evidence of ischemia, which would've existed in the angiographic arm alone, is not a proven therapy.	We used 40 to 70 percent when defining intermediate coronary stenosis in the introduction. We have used the cut-off of 50 percent to 70 percent as described by the evidence.
Peer Reviewer 6	Results	Page 17 lines 8 through 16: This is an example where mean FFR values for the different studies are recorded in a summary type fashion. 1 must keep in mind that FFR values are specific for each individual patient, and is more important to comment on the cut off values in each individual trial in this section rather than to summarize average values. The key point is, the trial showed that lesions are closed FFR was a ball of the cut off and did not benefit from having stenting procedures performed.	The data available are study-level, as described in each of these three studies. We have informed the readers that each of these studies used different thresholds of FFR for coronary stenting.
Peer Reviewer 6	Results	Page 17 lines 37 through 48: Is inappropriate to discuss acute QCA findings with respect to analyzing the benefit of FFR. the key point with respect FFR utilization in treating patients with these types of lesions is that the angiography, whether visually inspected or by QCA, is not a good enough surrogate. Therefore subsequently comparing MLD and other parameters to justify FFR results is inappropriate and should be deleted.	We have reported QCA data if available in individual studies evaluating FFR. The outcomes to be included in the report were finalized based on suggestions made by the technical expert panel members.
Peer Reviewer 6	Results	page 20 line 5: "Significantly" should read significant	Edited.
Peer Reviewer 6	Results	Page 27 line18:"off" should read of	Edited

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Results	Page 27 line 22: "Who may otherwise not undergo stent implantation"–I disagree with this statement. Context of the same trial was that frequently patient's undergo stent implantation for any angiographic stenosis of more than 50% narrowing. This is a clinical phenomenon which happens in the United States and Europe. While your statement is correct with respect to the evidence that supports this, it is not what is routinely followed in clinical practice.	We have deleted the sentence. We now conclude that the evidence for FFR was derived from trials that focused on patients with lower grade angina or those with nonischemic intermediate coronary stenosis. 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.
Peer Reviewer 6	Results	Page 35 line 9: While the statement is correct with respect to an FFR greater than 0.8 excluding ischemia, there should be consideration to comment that the best threshold for ischemia detection is an FFR of less than 0.75. This is also what the DEFER study used as there cut point. The modern same trial utilized 0.80 has been commented on throughout this document.	The interventions and comparators of interest were FFR- and angiography-guided stenting. When citing the evidence, we have used the threshold used in the FAME trial and in one other nonrandomized study. 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. Our review addresses the question of stenting a functionally significant stenosis for the comparison of FFR and angiography alone.
Peer Reviewer 6	Results	Page 48 LINE 56:as discussed above, this should read 40-70%	We have used the cut-off of 50 percent to describe the available evidence from one randomized trial.
Peer Reviewer 6	Results	Page 51 lines 28-48: as discussed above, there should be no comparison between QC A and FFR made. This point is not relevant.	We have reported QCA data if available in individual studies evaluating FFR. The outcomes to be included in the report were finalized based on suggestions made by the technical expert panel members.
Peer Reviewer 6	Results	Page 52 to line 25: mention should be made that the primary and point of the same trial was the composite outcome of death or myocardial infarction. All other endpoints are secondary and point.	We have amended the text to indicate that the primary endpoint was death, MI, and repeat revascularization.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Results	Figures 3 through 23: Care should be taken to format these figures in a similar manner in which favoring angiography and favoring IVIS remain on a consistent side either the left or the right. In reviewing these figures, they switch back and forth with respect to favoring I this guided being depicted on the right side of the figure in half of them while favoring high-risk guided strategy being depicted on the left side of the figure in the other half. This becomes a little bit confusing for the remainder.	This has been pointed out by many reviewers. The plots refer to opposite and very different outcomes (one is % diameter stenosis, which is the opposite of minimal lumen diameter). For example % diameter stenosis - lesser the stenosis is a better outcome. Similarly, for minimal lumen diameter, the bigger the diameter, the better the outcome. We have provided explanations as footnotes and have added arrows to indicate the direction of benefit.
Peer Reviewer 6	Results	Page 74 line 17: Suggest adding a statement stating that FFR and IVIS are complementary modalities that evaluate different aspects of coronary artery disease. As such not interchangeable and difficult to compare and head the head study.	Thank you. We have added your suggestion to the discussion.
Peer Reviewer 7	Results	On p16 line 28, I believe you intended to reference “50-70% stenosis” as intermediate, not >/=50%.	Thank you. We have amended the text.
Peer Reviewer 1	Discussion/ Conclusion	There is a nice summary of the key findings in this review which is also presented in tabular format. There is a comparison with recently published systematic reviews and comparison of current review with these prior reviews, including differences in the methodologies that led to differences in the studies included in the review. In particular, limitations in the current literature with regard to patient populations, clinical scenarios, contemporary data given quickly changing technology, and lack of data on specific intravascular diagnostic techniques are summarized. In particular, the section on evidence gaps nicely summarizes the key elements for which there are missing data and for which future research should be directed.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	Discussion/ Conclusion	FFR doesn't really measure blood flow is measures pressure drop at maximum hyperemia. Page ES-1 line 30: Authors overlook the issues that angiography often UNDER-estimates the stenosis severity thereby possibly deferring a clinically indicated revascularization procedure ES-1 line 35: Angiography also underestimate luminal dimensions after stent implantation ES-2 line 14: The is evidence that FFR can reduce costs by decreasing LOS (length of stay) and the need for stress testing ES-7: Authors shoud include and discuss the results of the DEFER study (JACC 2007;49:2105-11) ES-10 line 26: Should refer to "under-expanded" not "unexpanded" stents ES-10 line 54: Subacute stent thrombosis is not likely to be different in any study due to the extreme rarity of this event and the multifactorial causes	We have amended this sentence. We have added your suggestion Added. We have stated the findings in the results section. We did not find any evidence related to reduction in the need for stress testing, which was not part of the analytical framework. DEFER is not directly relevant to our questions, as the study combined the FFR-guided and angiography-guided stenting groups in the final analyses of outcomes. Nonetheless, we have cited this study in the background section. We have modified line 26 and line 54 on page ES-10
Peer Reviewer 4	Discussion/ Conclusion	Exceptionally well done. Gaps in evidence and future directions are very clear. Important to anticipate new trials reporting such as FAME-2.	Thank you.
Peer Reviewer 5	Discussion/ Conclusion	The implications of the major findings are clearly stated. The limitations of the study are clearly stated. In the discussion the authors cited appropriate studies. For the future studies the authors would need to discuss the future role of FFR in patients with bifurcation lesions, left main coronary artery stenosis, ostial LAD stenosis, acute coronary syndrome. In addition, they would emphasize that randomized studies are needed to assess the role of IVUS for stent optimization in the era of drug-eluting stents.	Thank you. We have added your suggestions in the future research section. The report already details the need for additional studies to assess the role of IVUS for stent optimization in the era of drug-eluting stents.
Peer Reviewer 6	Discussion/ Conclusion	Discussion seemed appropriately well-balanced and of the appropriate length.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 7	Discussion/ Conclusion	On p28 lines 37-39, I'm not certain that the potential advantages of IVUS guidance have become less significant with the use of DES. It may be that the advantages of IVUS guidance are more significant in a world where stent malapposition is a major predictor of stent thrombosis. Additionally, I suspect IVUS guidance may help increase the post-PCI MLA (through more directed post-dilation) and reduce edge dissections (through more appropriate upfront sizing of stent diameter and understanding of the plaque burden). I would consider rephrasing this statement-- both here and on p83 lines 33-36.	We have rephrased these sections.
Peer Reviewer 1	Clarity and Usability	As summarized in the earlier points, this is a well written, well structured and organized comparative effectiveness review on the use of intravascular diagnostic techniques versus angiography alone in patients with CAD undergoing PCI. The key questions are focused and clearly delineated with detailed and summarized presentation of the key findings in this review. The conclusions are succinctly summarized and may help inform clinical practice decisions and inform policy, although as pointed out in the review, with quickly evolving technologies, additional study is necessary to determine implications of these factors on policy decisionmaking.	Thank you.
Peer Reviewer 3	Clarity and Usability	The report is well structured and for the most part clear. I do feel more work and clarity is need before this document a=can be "used to inform policy and/or practice decisions." Utility of FFR in discovering when angiography under estimates lesion severity certainly needs to be discussed as does the times when IVUS and FFR are need together i.e. when angiography underestimates a lesion, FFR is discovers the lesion is significant but then IVUS may be needed to determine where to deploy a stent.	Thank you. We have added this to our discussion under the implications for clinical and policy decisionmaking subheading.
Peer Reviewer 4	Clarity and Usability	Absolutely. The most important recommendation is that new and emerging technology and techniques need to be evaluated and reported in a timely fashion. The technology should not be adopted until evidence is generated.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	Clarity and Usability	The report is well organized and structured. The key points are well written. In the conclusion the authors would need to state that implications for practice decision are limited because of paucity of data, in particular, with respect to IVUS for stent optimization in the era of drug-eluting stents. The authors would need to emphasize the need for future studies to expand the knowledge for assessment of high-risk patients with bifurcation lesions, ostial LAD lesions, and the left main stenosis.	We have made edits per your suggestion.
Peer Reviewer 6	Clarity and Usability	Overall document is clear, concise, and well reviewed. I would only ask that the following context to be considered for addition: The introduction of OCT and infrared spectroscopy have occurred very recently and clinical practice. These tools offer significant benefits which should be elucidated with respect to their ability to determine the anatomy and pathophysiology within the arterial lumen and it's plaque composition. Initial studies have suggested that these high-resolution imaging modalities show potential promise in the treatment of patient with coronary artery disease and we await evidence which supports the promise of these modalities.	The suggestions regarding OCT and infrared spectroscopy are already available in the report.
Peer Reviewer 7	Clarity and Usability	This report is very clearly presented and with the additional reference of the DEFER and FAME 2 studies as well as consideration of the clinical scenarios presented above, the results will be applicable to policy and practice decisions.	Thank you.
Volker Chris, St. Jude Medical	Recommendations	Key Question 1 - We recommend that the report state that there is "high" strength of evidence supporting the use of FFR to decide whether a coronary lesion requires intervention. Compared to angiography alone, FFR has demonstrated in multiple randomized clinical studies that FFR usage in PCI results in a lower risk of death or myocardial infarction, a decrease in the total length of hospital stay, fewer stents implanted and reduced costs. This recommendation is based on our review of the draft report, the available clinical literature on FFR, and clinical guidelines and appropriate use criteria that are based on clinical literature.	The use of FFR in clinical practice aids in therapeutic decision-making of intermediate coronary lesions. Based on our strict eligibility criteria, only one well-conducted trial comparing FFR with angiography alone was included. The level of evidence is based on the quality of eligible studies, and not the quantity of studies published.
Volker Chris, St. Jude Medical	Key Question 1	In evaluating this question, it appears the draft report mixes intravascular diagnostic technologies (FFR, IVUS, OCT, etc.) together even though the respective diagnostic techniques serve different purposes. We believe it would be more appropriate to review intravascular diagnostic techniques based on the type of information provided and the type of clinical decisions the diagnostic information is used to answer.	We have added that head-to-head comparisons may not be possible, because these techniques serve as complementary modalities during PCI.

Commentator & Affiliation	Section	Comment	Response
		Intravascular physiologic assessment techniques (i.e. FFR) should not be compared to intravascular imaging techniques (i.e. IVUS and OCT) as the techniques provide different types of information to answer different clinical questions. FFR provides a "go/no-go" decision in determining which lesions are ischemic and require intervention. OCT and IVUS generally provide morphological information related to stent placement (lesion characteristic, lesion length, lumen diameter, etc.) and stent evaluation (malapposition, strut coverage, etc.).	
		We believe the clinical literature and data related to FFR definitively demonstrate that there is a strong level of evidence that FFR can be used to assess whether or not a lesion is causing ischemia and requires intervention. In particular, the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study showed a large and significant reduction in adverse events when FFR was utilized compared to angiography alone. At oneyear follow up, the primary endpoint (composite of death, myocardial infarction and repeat revascularization) occurred in 18.3% of the angiography group and 13.2% in the FFR group (P=0.02) representing a 27.9% reduction in the FFR group. When compared to angiography alone, routine measurement of FFR during PCI reduced the rate of the composite endpoint of death, myocardial infarction, revascularization and CABG at one year by approximately 30%, and reduced mortality and myocardial infarction at one year by approximately 35%.	Thank you; all of the indicated findings are already detailed in the report.
		In the FAME trial, FFR was successfully measured in 94% of all lesions in the FFR-guided group. Procedure time in the FFR-guided group was equivalent, despite the addition of FFR measurements. Stent-related outcomes, such as rates of reocclusion and restenosis with FFR-guided stenting, as compared with stenting guided by angiography alone can be compared by referring to the need for repeat revascularization. At five years, 10.4% of patients in the FFR-guided group had one or more repeat revascularizations performed, 7.2% were related to a new or restenotic lesion and only 3.2% to an originally deferred lesion.	These findings are already covered in the report.
		Further, FFR has been shown to improve patient outcomes while concurrently providing cost savings, both at the time of	These findings are already mentioned in the report.

Commentator & Affiliation	Section	Comment	Response
		procedure and at one year. 1 The cost saving aspect of FFR is becoming increasingly important in the context of the rising costs of health care and continued focus on improved outcomes and appropriate use of therapies. The 2012 Appropriate Use Criteria (AUC) for Diagnostic Catheterization (developed by ACCF, SCAI and several related societies) puts forth several appropriate use criteria for diagnostic catheterization and PCI, including several appropriate uses for FFR as an "adjunct to coronary angiography for the determination of lesion severity and to assist in decisions about revascularization. As part of our review of the draft report, we noticed that several studies were excluded from consideration in the draft report. Typically, the excluded clinical studies were deemed to either have "No direct comparison between techniques" or were considered "Not relevant to KQs". We did not come to the same conclusion for these studies. Additional information regarding the specific studies excluded and our rationale on why we believe the respective studies should be considered in the draft report can be found in Exhibit I. We also strongly believe the DEFER (Deferral Versus Performance of Balloon Angioplasty in Patients Without Documented Ischemia) study should be included in the draft report. The DEFER study demonstrates the significant positive impact of utilizing FFR in assessing lesions and determining whether or not PCI is needed. The DEFER study showed that deferring PCI based on FFR measurement thresholds resulted in excellent long-term outcomes compared to performing PCI. The DEFER study demonstrated that the risk of cardiac death or myocardial infarction related to a functionally non-significant stenosis (as evidenced by a negative FFR test) is less than 1% per year and this risk was not decreased by stenting in this patient population (with negative FFR tests). The DEFER trial also demonstrated there were no major in-hospital adverse events in the group deferred from stenting based on FFR. In the stenting group, despite negative FFR values, the in-hospital event rate was 5.5%. At two years, there was also a significant benefit in terms of anginal class in favor of the Defer group. In the Defer group, no stent was implanted	 The references provided were reviewed against our eligibility criteria. Studies that clearly provided data for the FFR-guided stenting and angiography-guided stenting groups were included. The study did not meet our eligibility criteria because this study combined the FFR-guided and angiography-guided stenting groups to evaluate outcomes of therapeutic decision making, intermediate, and clinical outcomes. The DEFER trial examined appropriateness of stenting a functionally nonsignificant stenosis and did not compare FFR-guided stenting versus stenting guided by angiography alone Our comparisons of interest were FFR use versus no FFR use in stenting. We did not find that comparison group in this study. The FAME trial is the only RCT that utilized a comparison of FFR use versus no FFR use in stenting.

Commentator & Affiliation	Section	Comment	Response
		and PCI was deferred based on a negative FFR test. Additional FFR studies were excluded with the reason noted as “no direct comparison between techniques”. We do not agree with this reason for excluding the studies listed in Exhibit I. In clinical practice, angiography is performed in all PCI procedures and additional intravascular diagnostic techniques are utilized as necessary in addition to angiography. This is consistent with patients included in the various FFR trials – all patients were assessed by angiography, and then patients received FFR per protocol requirements. Inherently, there is a comparator to angiography alone in that clinical decisions were made based on the patient initially being assessed via angiography, and then the angiographic assessment was either validated or altered based on the FFR results. We believe that to exclude the studies noted in Exhibit I because of no comparator is inappropriate given angiography was always performed in these trials in every procedure. Both guidelines and AUC indicate that a stenosis should not be stented unless it is the cause of ischemia.2 3 In addition, the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention4 states that: ☐ The limitations of coronary angiography for determination of lesion severity have been well established ☐ Angiography may under or over estimate lesion stenosis ☐ The correlation of ischemia on stress testing with FFR values of < 0.75 has been established in numerous comparative studies with high sensitivity (88%), specificity (100%), positive predictive value (100%), and overall accuracy (93%) ☐ Fiveyear outcomes for patients treated with medical therapy (based on an FFR > 0.75) were superior compared with PCI outcomes in the DEFER study ☐ The FAME study identified the benefit for deferring PCI in patients with multivessel disease and lesion FFR > 0.80, with reduced rates of cardiac events at both one and two years. The ESC/EACTS guidelines have rated FFR-guided PCI as “IA” for detection of ischemia-related lesion(s) when objective evidence of vessel-related ischemia is not available. This is the highest rating provided by these guidelines. Furthermore, the ACCF/AHA/SCAI guidelines have rated FFR as having a level of evidence “A” (the highest rating for level of evidence) for	This report has covered all the points that are stated here. Our report does not compare the role of PCI versus medical therapy. The evaluation of diagnostic accuracy of FFR is not part of scope of this report. This report evaluates outcomes of therapeutic decisionmaking, intermediate, and clinical outcomes based on a good diagnostic accuracy data from the use of FFR.

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		assessment of one or more significant stenoses amenable to revascularization and unacceptable angina despite guideline-directed medical therapy. A summary of the clinical literature on FFR from which the ACCF/AHA/SCAI guidelines are based is included as Exhibit II. In reviewing the clinical data for FFR and the guidelines and AUC based on the respective clinical data related to FFR, we recommend that the evidence level for the use of FFR in determining whether to treat a lesion should be reclassified from "moderate" to "high".	Again, revascularization versus medical therapy is not a comparison of interest for the purposes of this report. The FAME trial is the only RCT that utilized a comparison of FFR use versus no FFR use in stenting. The evidence rating provided in this report is for the aforementioned comparison only.
Volker Chris, St. Jude Medical	Key Question 2	For this question, we were somewhat confused regarding what is meant by "to guide stent placement." If stent placement includes determining which lesions require PCI, then FFR has a clear role for reasons explained in Key Question 1. In addition, FFR can impact stent placement decision-making for complex cases such as serial/tandem stenoses and jailed side-branch lesions in which stenting of one lesion changes the functional significance (but not necessarily the angiographic or anatomical appearance) of another lesion. If, however, "to guide stent placement" refers to when the decision has been made to perform PCI, then intravascular imaging is relevant in making determinations such as stent diameter and length and other criteria for stent placement, guidance and assessment. We agree with the draft report in regards to the level of evidence for IVUS in determining the impact of using intravascular imaging to guide stent placement. In addition, we believe that OCT images provide the same general types of information as IVUS and that OCT images inform the same clinical questions that IVUS does. However, OCT images provide much greater detail and are easier to interpret for clinical decision making.9 The clinical publications noted in Exhibit III demonstrate that OCT provides similar clinical decision-making information as IVUS.	We chose specific wording to draw a distinction between the key question 1 and 2: the decision whether or not to stent (KQ1) and how to place the stent once the decision to stent has been made (KQ2). Studies evaluating FFR addressed KQ1 and studies evaluating IVUS addressed KQ2. High-definition images of OCT provide valuable information during stenting, and OCT has shown promising results in initial studies. However, the comparison of interest for this report was the use of an intravascular imaging technique versus no use, and we did not find an OCT study that addressed this comparison.

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Volker Chris, St. Jude Medical	Key Question 3	The draft report indicates that there is insufficient evidence to evaluate FFR's ability to assess the success of stent placement immediately after PCI. FFR immediately after stenting has been shown to be a strong independent predictor of outcomes. This was demonstrated in a study published in 2002. This study was excluded in the draft report (Pijls NH, Klauss V, Siebert U, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation 2002 Jun 25; 105 (25):2950-54; listed on page B-32 of the report). We believe this clinical study was incorrectly excluded as the study does provide a comparison of FFR to angiography alone, and we recommend this study for inclusion in the report. More recently, Nam et al showed that the one-year clinical outcomes after DES implantation correlated with FFR measurements10 demonstrating that lower FFR measurements were predictive of higher adverse event rates. We believe this study should be included in the review also. Both studies are listed in Exhibit I. FFR measurements pre- and post placement of stents provide critical information regarding the severity of stenosis of a lesion and assess the success of the stent in decreasing ischemia and restoring blood flow. Similar to the value that FFR provides in clinical decision making to determine which lesions require intervention prior to PCI, FFR can also be used to evaluate the success of stent placement immediately after PCI. After a stent is placed, an FFR measurement can be taken to confirm that ischemia has been adequately treated or whether further intervention is required (for example, if there are additional/serial lesions that may also be the cause of ischemia).	The comparison of interest for this report was the use of an intravascular imaging technique versus no use. We did not include studies that solely compared revascularization versus medical therapy, or different FFR thresholds. We have added a statement clarifying this in our methods section. Citation 2 (Wongpraparut et al.) in Exhibit I is already included in this report. Similarly, Nam et al., 2010, is already included in the report. We agree with your statement. We reviewed evidence when available for all Key Questions.

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Volker Chris, St. Jude Medical	Key Question 4	As stated earlier in our comments, we believe a distinction should be made when evaluating this key question based on the type of information that specific intravascular diagnostic techniques are intended to provide and the type of clinical decisions the respective techniques inform. We believe it is inappropriate to compare FFR to intravascular imaging as these technologies serve different purposes in clinical decision making. For intravascular imaging, we believe there is "moderate" strength of evidence when comparing IVUS and OCT in that both imaging techniques provide the same general type of information. In evaluating the clinical evidence, we found three studies that were omitted from consideration as listed in appendix B to the draft report and two additional studies that compare IVUS and OCT. These studies are listed in Exhibit III. These studies in Exhibit III demonstrate that OCT is at least as effective as IVUS in evaluating stent positioning. Additionally, based on these and various other studies, a consensus document was recently published in JACC by the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation11. The Working Group consists of experts in intravascular OCT from Asia, Europe, and the United States. This group developed a table that summarizes the Working Group's assessment of the level of evidence for OCT to assess the respective lesion, vessel and stent characteristics. The consensus document notes that there is a high evidence level for most of the criteria, and the summary table of the consensus document is included as Exhibit IV.	The Key Questions were developed and refined with the help of experts in the field. The diagnostic versus imaging technique questions were retained following this processes. We have added a statement clarifying that these complementary techniques are utilized for different purposes during PCI. The studies included in Exhibit III did not meet the eligibility criteria for the comparison of use of an intravascular imaging technique versus no use. We did not include studies in which all patients underwent both IVUS and OCT. We did not include studies that were conducted solely for diagnostic accuracy. We have added text to clarify that initial studies have suggested that these high-resolution imaging modalities show potential in the treatment of patient with coronary artery disease, and that we await evidence which supports the promise of these modalities.

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Volker Chris, St. Jude Medical	Key Question 5	In evaluating this question, we were confused in terms of what specifically was meant regarding patient characteristics. For FFR, both the DEFER and FAME clinical studies provide details on patient populations through the protocol inclusion criteria and the baseline characteristics of the patients enrolled. Some of these characteristics include the percentage of patients with hypertension, diabetes, previous myocardial infarction, angina classification and smoking history. Improved patient-centered outcomes from FFR have been demonstrated in a wide variety of patient subsets, including stable, ACS and diabetic, with and without prior non-invasive testing, patients with prior myocardial infarction, patients with coronary artery bypass grafts; as well as a broad range of lesion subsets including single and multivessel disease, serial and bifurcation lesions, ostial lesions, proximal LAD and left main lesions and diffuse disease.	We included studies that evaluated patient-level characteristics either in stratified analyses or through interaction tests for the comparison of use of an intravascular imaging technique versus no use.
Volker Chris, St. Jude Medical	Future Research Needs	The draft report provides information on future research needs for intravascular diagnostic techniques. As noted in the draft report, intravascular diagnostic techniques are quickly evolving, as is the clinical literature to demonstrate the impact of these technologies. One study that we believe will have a significant impact on clinical practice regarding PCI is the FAME II trial. The purpose of FAME II is to compare the clinical outcomes (a composite of all cause death, documented MI, unplanned hospitalization leading to urgent revascularization), safety and cost effectiveness of FFR-guided PCI plus optimal medical treatment (OMT) versus OMT alone in patients with stable coronary artery disease. FAME II will also demonstrate the impact of FFR on non-urgent revascularizations. While FAME II is mentioned in the "Ongoing Research" section of the report, we recommend that the report should be updated with additional data from FAME II when the data is presented and published in the coming months. Enrollment in FAME II was recently halted early by the DSMB (data safety and monitoring board) due to the significant benefit shown in the FFR arm of the study as compared to the OMT arm. Additional information on the FAME II study is included in Exhibit V. In addition, we recommend that the report be updated with the five-year results of the FAME study which will be presented and published in the near future. The FAME five-year data will provide additional valuable insight into the long-term outcomes	The FAME II trial is not eligible for this report because it compares medical treatment versus revascularization. Nonetheless, this study's eligibility criterion is discussed in the results section of report without being included in the evidence. We have removed this study from the ongoing research section.

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		associated with FFR. The evidence supporting OCT also continues to increase rapidly as clinicians better understand how the high resolution images provided by OCT can inform clinical decision making and affect patient outcomes. For example, in May, 2012, two studies were presented that compared the use of OCT to other intravascular diagnostic techniques. The first, a multicenter, retrospective, case matched study of 670 patients, compared angiography to angiography plus OCT. The second, a multicenter, prospective randomized study of 100 patients, compared the reliability and feasibility of OCT to IVUS in coronary lesion assessment. These studies provide evidence that directly answers some of the Key Questions in this comparative effectiveness review and are included in Exhibit III. Because of the speed at which intravascular diagnostic techniques are evolving and that new compelling clinical studies will be available in near future, we urge that AHRQ update this comparative effectiveness review with the clinical studies mentioned above and also that the review should be updated within the next two to three years for additional clinical studies.	Thank you. Our update search did not identify these studies. Thank you.