

## HTA-Report | Summary

# Measurement of fractional flow reserve to guide decisions for percutaneous coronary intervention

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## Background

Coronary artery disease (CAD) is one of the leading causes of premature death in Germany and other developed countries. It is attributed with a high societal burden of disease as a result of loss of productivity and hospitalization.

CAD can cause stenoses of the coronary arteries that lead to an insufficient oxygen supply of the myocardium. One of the leading symptoms of CAD is (exercise-dependent) chest pain (angina pectoris). Various diagnostic procedures are available for the assessment of the functional relevance of coronary stenoses: stress-ECG, stress-echocardiography, scintigraphy, and positron emission tomography (PET). Coronary angiography is the predominant technique being used and yields, as well as cardiac magnetic resonance tomography and intravascular sonography morphologic information.

CAD can be treated effectively with medication and/or percutaneous coronary interventions (PCI). PCI restores sufficient blood flow via a catheter-based angioplasty with or without stenting. The use of stents has substantially increased in recent years. However, the necessity of PCI has not been proven for all patients. Particularly, in the absence of pre-documented ischemia, the effectiveness of PCI is unknown.

Coronary pressure-based fractional flow reserve (FFR) is an invasive test that measures the pressure gradient across the coronary stenosis, allowing one to assess the functional relevance of the stenosis and the potential causal role of the stenosis in chest pain.

## Research questions

The objective of this study was to assess the clinical effectiveness and the cost-effectiveness of FFR-based versus universal performance of PCI in patients with chest pain but without documented coronary ischemia.

In severe stenoses, there is a clear correlation between morphological and functional findings. However, there is uncertainty regarding the diagnosis and treatment of intermediate stenoses (i. e., a 40 to 70% reduction in lumen diameter). The risks and benefits with respect to survival, immediate and medium-term complications, health-related quality of life and economic consequences must all be weighted when a decision is made in those patients.

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Therefore, this HTA report (HTA = Health Technology Assessment) addresses the following research questions:

1. What is the diagnostic accuracy of FFR testing compared to a reference standard.
2. What are the clinical benefits and risks of FFR testing compared to current practice?
3. What are the economic consequences of FFR testing in the context of the German healthcare system?
4. What is the cost-effectiveness of FFR testing compared to current practice?

## Evaluation of clinical effectiveness

### Methods

A systematic literature search of electronic databases (MEDLINE EMBASE, ECONLIT, Cochrane- databases, common HTA-databases) was performed. The search was supplemented with references from relevant articles and expert advice. Publications that addressed physiological foundations, practical questions or technical aspects, case studies or series, narrative reviews as well as comments, editorials and studies only published as abstracts were all excluded. Additional exclusion criteria were defined for particular research questions (diagnostic accuracy or economic studies). Relevant studies were depicted using systematic evidence tables. Study quality was assessed using DIMDI instruments (Deutsches Institut für Medizinische Dokumentation und Information/German Institute for Medical Documentation and Information). In diagnostic studies, parameters of test performance were extracted and used to calculate 2-by-2 tables. A meta-analysis was performed in order to calculate pooled estimates for sensitivity and specificity. Sensitivity analyses were used to assess the influence of single studies. Subgroup analyses were performed in order to evaluate the influence of disease severity, choice of reference standard, and other relevant factors.

### Results

In total, we included twelve studies relevant to this HTA-report including ten diagnostic accuracy studies of FFR measurement, one randomized clinical trial (RCT) investigating the clinical benefit of an FFR-based treatment strategy, and one economic evaluation.

The mean quality score for the diagnostic studies was 8.6 out of 14 points (range: seven to 10.5 points). Our meta-analysis included a total of 717 patients/coronary lesions. Most studies had been performed in Europe though there were several from Japan and the US as well. Studies took place between 1994 and about 2004. Patients were predominantly male in all studies (62 to 95%) and had a mean age of between 53 and 65 years. In six of nine studies, single photon emission computed tomography (SPECT) was used as a reference standard. Pooled sensitivity was 81.7% with a 95% confidence interval (95% CI) of 77.0-85.7%. Pooled specificity was 78.7% (95% CI: 74.3-82.7%). Sensitivity analyses showed that the results were robust. Subgroup analyses indicated that the type of reference standard (SPECT vs. non-SPECT) and disease severity (single-vessel-disease vs. multi-vessel disease) were potentially influential factors. However, due to limited sample size in the respective subgroups, results were not affected in a relevant extent.

The RCT that investigated the clinical benefit of an FFR-based treatment

strategy was a multicenter study of 325 patients who had no documented history of myocardial ischemia. This study demonstrated that, in patients without functional stenosis ( $FFR \geq 0.75$ ), FFR testing is more effective than universal PCI when examining freedom of symptoms after two years and is at least as effective as universal PCI when examining major adverse cardiac events.

## Discussion

The pooled estimates for FFR test performance were found to be relatively precise and robust, although single studies demonstrated a potential for bias. Univariate sensitivity analyses showed type of reference standard and severity of disease as influential factors. If more studies of FFR testing become available, the effect of these variables should be investigated further using meta-regression techniques. Because the included studies covered a large range of disease severity and contexts, the external validity and generalizability is likely to be good.

The only relevant RCT confirmed the clinical effectiveness of an FFR-based treatment strategy for patient-relevant endpoints such as angina status and major adverse cardiac events.

## Economic evaluation

### Methods

The literature search was performed in a similar manner to the clinical literature search in that electronic databases (MEDLINE EMBASE, ECONLIT, Cochrane-databases, common HTA-databases) and expert advice were used. The description of studies and evaluation of study quality was performed using the DIMDI instruments.

### Results

Only one economic evaluation of FFR-based treatment strategies was identified and included. In this evaluation, Fearon and colleagues developed a decision-tree model to compare the long-term health effects and costs of three strategies for treating patients with an intermediate coronary stenosis and no prior functional (i.e., hemodynamic) test in the US healthcare context. The strategies examined included: 1) nuclear stress imaging testing to guide the decision on PCI, 2) FFR testing to guide the decision on PCI, and 3) universal PCI in all patients. The authors adopted the societal perspective (without consideration of indirect costs) and used a lifetime horizon for their evaluation. The target population consisted of 55 year-old patients with chest pain and angiographically determined intermediate stenosis without documented myocardial ischemia. The analysis was restricted to patients with single-vessel disease.

Results were presented as discounted incremental cost-utility ratios (ICUR) of the FFR-strategy as compared with the two other strategies. Data for diagnostic test performance were derived from two diagnostic studies, data for treatment efficacy from a meta-analysis, the duration of treatment effects from two randomized clinical trials, mortality associated with the procedures from a large cohort study, and utilities from one cross-sectional study. The estimate of the remaining life expectancy was based on the results of a published decision analysis performed in 1999. Cost data were based on the published literature, manufacturer information, professional fee tables, and hospital accounting data. All cost data were converted to 2000 US dollars (USD). Costs and health effects were discounted by 3% per year.

After discounting, the FFR-based strategy resulted in 14.7940 QALY and lifetime costs of 11,395 USD per patient, the nuclear stress test-based strategy resulted in 14.7962 QALY and costs of 13,190 USD, and universal PCI resulted in 14.7761 QALY and costs of 15,225 USD. Hence, universal PCI was dominated by both the FFR strategy and the nuclear stress test strategy because it was more costly and less effective. The discounted ICUR for the nuclear stress test strategy as compared to the FFR test strategy was 808,000 USD/QALY. Sensitivity analyses indicated robust results. The authors concluded that measurement of FFR as a guide for decisions regarding PCI in patients with an intermediate coronary lesion and no prior functional test may lead to significant cost savings as compared with the performance of nuclear stress imaging or universal PCI in all patients.

## Discussion

Only one economic study was identified. This study employed a straightforward approach and a simple decision tree, utilizing quality-adjusted life expectancy as a health outcome and relying on several simplifying assumptions. A particular strength of this study was the inclusion of a noninvasive imaging test as an alternative to FFR testing and sensitivity analyses of the diagnostic performance of both tests.

Overall this study is the first decision analysis in this area. It should be replicated for other countries using a more detailed modeling approach with actual units and prices. Because this study was performed in the US healthcare context where price patterns of coronary stents differ significantly from Germany, these results are only of limited value for a German assessment. It was thus necessary to develop a decision-analytic model for the German healthcare context.

## Decision-analytic model

### Methods

We developed the German Coronary Artery Disease Outcome Model (German CADOM), a decision-analytic Markov model, to estimate the long-term effectiveness and cost-effectiveness of FFR measurement to guide the decision on PCI in the context of the German healthcare system.

We modeled the long-term clinical and economic consequences of two alternative strategies in patients with single-vessel disease without documented myocardial ischemia: 1) FFR testing to guide the decision on PCI (FFR-TEST) and 2) universal treatment with PCI in all patients (UNIVERSAL). The model combines a decision tree for diagnostic and short-term outcomes with a seven-state Markov model for long-term events. The Markov model includes the Markov states of “no angina,” “mild angina,” and “severe angina conditional on prior PCI” as well as the absorbing state death. Cycle length was one year. We adopted the societal perspective and a lifetime analytic time horizon.

Prevalence data and data for short-term treatment outcomes were based on a randomized clinical trial with a two-year follow-up. Data on progression and incidence of revascularizations, short- and long-term mortality of interventions, and utilities were extracted from published studies. Cost data were extracted from the German CAD Cost Database. Prices for medications followed the German “Rote Liste.”

We then calculated the remaining life expectancy, QALY, lifetime costs and the discounted ICUR. In addition, we performed extensive univariate and multivariate sensitivity analyses and subgroup analyses (gender, age: 30 to 70 years).

## Results

Based on the results of our decision analysis using the German CADOM, the FFR-TEST strategy improves the discounted quality-adjusted life-expectancy for 60-year old men (basecase analysis) by 5.0 quality-adjusted life days (QALD) when compared to the UNIVERSAL strategy. FFR-TEST improves undiscounted life expectancy by 6.6 days when compared to UNIVERSAL. In this population, FFR-TEST increases discounted lifetime costs by 214 Euro per patient compared to UNIVERSAL. The discounted ICUR for FFR-TEST versus UNIVERSAL is about 16,000 Euro per QALY gained.

Subgroup analyses demonstrated no decision-relevant differences by gender but provided evidence that the results differ across age groups. For a mixed population such as that observed in the DEFER Study (71% men, 29% women), the ICUR was 16,000 Euro/QALY for 60 year-olds, 25,000 Euro/QALY for 50-year olds, 31,000 Euro/QALY for 40-year olds, and 35,000 Euro/QALY for 30-year old patients. FFR-TEST dominates UNIVERSAL for 70 year-old patients.

One-way sensitivity analyses for re-stenosis risk in the target lesion, PCI-related peri-procedural mortality, effects of the PCI on long-term survival, relative mortality risk for functional versus nonfunctional stenosis, and coronary stent price are robust under conservative assumptions (bias against FFR testing). The ICUR significantly depends on the price of the FFR test (basecase price: 555 Euro). If the basecase price is halved, FFR-TEST would become the dominant strategy, whereas if the price is doubled, this would make FFR-TEST economically less attractive. The most influential sensitivity analysis parameters were 1) the relative reduction in long-term mortality after PCI in patients with non-functional stenosis and 2) the prevalence (prior probability) of functional stenoses. For patients with a low probability of functional stenosis (<17%), FFR-TEST is dominant, whereas for patients with a high probability of functional stenosis (>68%), FFR-TEST becomes economically less attractive (ICUR>50,000 Euro/QALY). If PCI does not have any beneficial effect on mortality for non-functional stenoses, the ICUR for FFR-TEST is 7300 Euro/QALY. For a PCI-related mortality reduction of 14.3% or higher in non-functional stenoses, UNIVERSAL dominates FFR-TEST.

## Discussion

Based on our decision analysis, the use of FFR measurement to guide the decision on PCI should result in better health outcomes than universal use of PCI in patients with chest pain and single-vessel disease without documented myocardial ischemia. The FFR-based strategy should also be cost-effective when compared to other well-accepted medical interventions.

We identified only one other published study that investigated the cost-effectiveness of FFR measurement in CAD patients, though it was performed for the US healthcare context. This study showed greater clinical benefit associated with FFR measurement than was demonstrated in our study. This can be explained by the fact that the US study was based on a decision tree analysis with simplifying assumptions, whereas our decision analysis used a Markov model. This allowed us to explicitly and transpar-

ently model the effects of interventions on the long-term course of the disease, the progression of angina and quality of life. Our model was built on explicit and extremely conservative assumptions in favor of the long-term benefit of PCI (bias against FFR measurement). In addition, in the US study the FFR-based strategy was less costly than universal PCI, whereas our conservative German basecase analysis demonstrated FFR testing to be cost-effective, but slightly more expensive than universal PCI. This can be explained by our conservative long-term assumptions in favor of universal PCI as well as by lower stent prices in Germany as compared to the US.

The most relevant limitations of our study are that data are currently available only for short time horizons and are not stratified by functional versus non-functional stenoses when reported. In addition, essential parameters are derived from a single RCT with limited numbers of patients. Given that we have used extremely conservative model assumptions, we expect that the real effect of FFR measurement as a guide for decisions about PCI is more beneficial and cost-effective than our estimates suggest.

### **Ethical, social and legal aspects**

Our literature search did not yield any publications addressing ethical, social or legal aspects of the FFR technology relevant to the research questions of this HTA-report.

### **Summary discussion of all results**

This HTA report is the first comprehensive and systematic review of FFR technology. Based on the diagnostic meta-analysis in this report, FFR should be a valid test with a good diagnostic performance. The only published RCT that investigated the clinical benefit of FFR measurement showed that, in patients without documented myocardial ischemia, an FFR-based strategy is at least as effective as universal PCI in all patients. The only economic evaluation demonstrated that, in the US healthcare context, an FFR-based strategy is more effective and less costly than universal PCI. Due to different cost structures, the US results cannot be transferred to the German context. Therefore, we developed the German Coronary Artery Disease Outcome Model (CADOM) in order to estimate the long-term effectiveness and cost-effectiveness of FFR measurement in the German healthcare context. Based on our decision analysis in patients with chest pain and single-vessel disease without documented myocardial ischemia, FFR measurement as a guide for decisions regarding PCI should be effective and cost-effective in the German context.

This HTA-report demonstrates that diagnostic studies of test performance, RCT assessing short-term clinical benefits, epidemiologic studies examining long-term outcomes, quality-of-life studies determining patient preferences, and economic studies cannot be judged in isolation. All data relevant to the decision problem and the time horizon of interest must be critically assessed for their quality and then incorporated in a decision-analytic model that evaluates the short- and long-term clinical benefit and cost-effectiveness in the healthcare context of interest. This must also be accompanied by a comprehensive uncertainty assessment such as that of a sensitivity analysis.

This HTA-report has several limitations. Most of the diagnostic studies have failed to apply a valid gold standard as a reference. Many of the studies also have the potential of further bias, for example, progression bias. Only one RCT investigating the clinical benefit of FFR testing in the decision context has been published. This RCT did not prove the superiority of either of the

compared strategies with statistical significance. This study also used major adverse cardiac events as the combined endpoint. Due to a limited sample size and a follow-up period of two years, no inference on mortality effects can be drawn. The latter is only possible using a decision-analytic approach. Some of the parameters of the decision-analytic model have been taken from registries that may not adequately reflect current healthcare realities. Moreover, progress in interventional cardiology is rapidly advancing and more extensive data on new technologies such as the long-term efficacy and safety of drug-eluting stents are not yet sufficient to draw final conclusions. In particular, data on the effectiveness of PCI stratified by functional status of stenosis are lacking. Such questions must be answered in further research, in which large database registries will play an important role.

As a result of limited available evidence, this HTA-report has been restricted to an assessment of the impact of FFR measurement in patients with single-vessel disease. However, FFR measurement can have an important role in multi-vessel disease by guiding the decision as to whether and which coronary lesions should be stented. Clinical investigation in this area is ongoing and should be incorporated into the clinical, economic and decision-analytic assessment, once these results are available.

### **Conclusions and recommendations**

Based on both current evidence and the results of decision-analytic modeling, the use of FFR measurement to guide the decision on PCI should lead to better short- and long-term clinical outcomes in patients with stable angina and single-vessel disease without documented myocardial ischemia and it should provide a cost-effective use of resources in the German healthcare system. Therefore, FFR measurement should be introduced in routine clinical decision making along with appropriate reimbursement strategies in order to avoid wrong incentives.