ORIGINAL RESEARCH

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Comparing treatment outcomes of fractional flow reserve-guided and angiography-guided percutaneous coronary intervention in patients with multi-vessel coronary artery diseases: a systematic review and meta-analysis

Abstract

Purpose: Fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) is used to assess the need for angioplasty in vessels with intermediate blockages. The treatment outcomes of FFR-guided *vs.* conventional angiography-guided PCI were evaluated in patients with multi-vessel coronary artery disease (CAD).

Methods: Prospective and retrospective studies comparing FFR-guided *vs.* angiography-guided PCI in patients with multi-vessel CAD were identified from medical databases by two independent reviewers using the terms “percutaneous coronary intervention, fractional flow reserve, angiography, coronary heart disease, major adverse cardiac events (MACE) and myocardial infarction”. The primary outcome was the number of stents placed, and the secondary outcomes were procedure time, mortality, myocardial infarction (MI) and MACE rates.

Results: Seven studies (three retrospective and four prospective), which included 49,517 patients, were included in this review. A total of 4,755 patients underwent FFR, while 44,697 received angiography-guided PCI. The mean patient age ranged from 58 to 71.7 years. The average number of stents used in FFR patients ranged from 0.3-1.9, and in angiography-guided PCI patients ranged from 0.7-2.7. Analysis indicated there was a greater number of stents placed in the angiography-guided group compared with the FFR group (pooled difference in means: -0.64, 95% confidence interval [CI]: -0.81 to -0.47, $P < 0.001$). There were no differences in the secondary outcomes between the two groups.

Conclusions: Both procedures produce similar clinical outcomes, but the fewer number of stents used with FFR may have clinical as well as cost implications.

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Fractional flow reserve (FFR) is a valuable tool for assessing the functional significance of coronary artery stenosis in patients with multi-vessel coronary artery diseases (CAD). It is defined as the ratio of maximal achievable blood flow in a stenotic artery to the hypothetical maximal achievable blood flow in the same artery in the absence of stenosis [1]. FFR provides a direct estimate of coronary blood supply independent of heart rate, blood pressure or contractility changes, and has prognostic significance in various clinical settings [2-5]. It is determined by calculating the ratio of distal coronary pressure measured with a coronary pressure guide wire, to the aortic pressure measured simultaneously with the guiding catheter. FFR in a normal coronary artery is 1.0 and a $\text{FFR} \leq 0.80$ was reported to identify ischemia-causing coronary stenosis with more than 90% accuracy [6]. Together with coronary flow reserve, FFR can provide information about the epicardial artery and the microvascular bed it subtends [7]. FFR-guided percutaneous coronary intervention (PCI) has been shown effective even in small coronary artery stenosis [8]. Furthermore, it has been proven to be cost-saving [6,9,10]. However, it is still unclear whether routine measurement of fractional flow reserve in addition to angiography improves clinical outcomes [6].

In patients with multi-vessel CAD undergoing PCI coronary angiography is the standard method for guiding stent placement. FFR-guided PCI has the potential to overcome limited spatial resolution and poor specificity which has plagued other non-invasive functional tests for patients with multi-vessel CAD. The FAME (Fractional Flow Reserve Versus Angiography for Multi-vessel Evaluation) study showed that the routine use of FFR in addition to angiography improves outcomes of PCI at 1 year follow-up [11]. Measurement of FFR has a high impact on clinical decision-making in the catheterization laboratory, as it can be used to reclassify patients with multi-vessel stenoses, reducing the need for revascularization in the majority of cases [12]; however, since the value of FFR is influenced by stenosis severity, as well as the amount of viable myocardium subtended by the coronary branch harboring the stenosis, similar lesions might have a completely different functional significance based on FFR, depending on the location and size of the stenosis [13].

The present meta-analysis aimed to compare treatment outcomes of FFR-guided PCI *vs.* the current practice of treatment guided solely by angiography in patients with multi-vessel CAD. The outcomes examined included the number of stents required, procedure time and the rate of major adverse cardiac events (MACE).

Materials and Methods

Selection criteria

A literature search of the Medline, Cochrane, EMBASE and Google Scholar databases were performed until June 26, 2014 using the terms “percutaneous coronary intervention, fractional flow reserve, angiography, coronary heart disease, major adverse cardiac events and myocardial infarction”. Prospective and retrospective studies comparing FFR- *vs.* angiography-guided PCI in patients with multi-vessel CAD, with at least one measurable outcome were selected. Non-English articles, letters, comments, editorials, case reports, proceedings and personal communications were excluded. Studies with no quantitative primary or secondary outcomes were also excluded. Studies were further subgrouped according to their prospective or retrospective nature.

Outcomes and definitions

The primary outcome measure was the number of stent placements, while the secondary outcomes included procedure time, mortality and the MACE rate. MACE was defined as the composite of death, myocardial infarction and any repeat revascularization.

Data extraction

Studies identified by the search strategy were hand-selected and data extracted by two independent reviewers. Where there was uncertainty regarding eligibility, a third reviewer was consulted. The following information was extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each treatment group, participants' age and gender, patient type, primary and secondary outcomes, as well as the length of follow-up. After full text review, studies were excluded for following reasons: no outcome of interest ($n = 13$), one-arm study ($n = 4$) and same as another article ($n = 2$).

Quality assessment

The Cochrane Risk-of-Bias Tool, a component of Review Manager 5.1 [14], was used to assess the quality of the included studies. Quality assessment was also performed by two independent reviewers and a third reviewer was consulted to resolve any uncertainty.

Statistical analysis

For the number of stents used and the procedure time, means with standard deviation were calculated and compared between the FFR- and the angiography-guided PCI groups.

Crude or adjusted hazard ratio (HR)/relative risk (RR) with 95% confidence intervals (CIs) were calculated for mortality, rate of myocardial infarction (MI) and the MACE rate for each individual study and for all the studies combined. A χ^2 -based test of homogeneity was performed and the inconsistency index (I^2) and Q statistics were determined. If the I^2 statistic was $>50\%$, a random-effects model was used. Otherwise, a fixed-effects model was employed. Pooled effects were calculated and a 2-sided P value < 0.05 was considered statistically significant. In addition, subgroup analysis of treatment effectiveness was performed according to the study type, prospective/randomized controlled trial (RCT) or

non-RCT. Sensitivity analysis was carried out using the leave-one-out approach. All analyses were performed using Comprehensive Meta-Analysis software, 2.0 (Biostat, Englewood, NJ, USA).

Results

Literature search

A flow diagram of study selection is shown in Figure 1A. After initial screening and removal of duplicates, 32 articles were identified based on eligibility and six were excluded based on the inclusion/exclusion criteria. After reviewing the full texts of the remaining 26 articles, 19 were excluded and the reasons for exclusion are shown in Figure 1A. A total of seven articles were included in the meta-analysis [8, 11, 15-19].

TABLE 1. Summary of study characteristics

First author (year)	Study Design	Type of patients	Number of vessels involved	Comparison	Number of patients	Age (years)	Male (%)	Duration of follow-up (years)
Pijls (2010) [11]	RCT	Multivessel CAD undergoing PCI	Multivessel	Angio-guided	496	64.2	73%	2
				FFR-guided	509	64.6	75%	
Koo (2008) [15]	Prospective	Coronary bifurcation lesions with jailed side branches after DES, drug eluting stent implantation at the main branches	Multivessel	Angio-guided	110	63	70%	0.5
				FFR-guided	110	62	68%	
Wongpraparut (2005) [16]	Prospective	Multivessel CAD	Multivessel	Angio-guided	80	62	79%	2
				FFR-guided	57	58	75%	
Frohlich (2014) [17]	Cohort	Patients undergoing PCI	Multivessel	Angio-guided	37090	65.8	74.3%	3.5
				FFR-guided	2767	64.2	73.9%	2.3
Li (2013) [18]	Retrospective	Coronary revascularization with or without adjunct FFR	At least one vessel	Angio-guided	6268	67.9	70.4%	7
				FFR-guided	1090	65.7	62.6%	
Di Serafino (2013) [19]	Retrospective	Coronary angiography for stable or unstable angina	At least one vessel	Angio guided	158	71	77%	4
				FFR guided	65	69	77%	
Puymirat (2012) [8]	Retrospective	with PCI for stable or unstable angina in small native coronary vessels	One coronary vessel	Angio-guided	495	71.7	68%	3.3
				FFR-guided	222	71.6	58%	

Abbreviations: RCT = randomized controlled trials; CAD = coronary artery diseases; PCI = percutaneous coronary intervention; FFR = fractional flow reserve; and, Angio = angiography.

TABLE 2. Summary of primary and secondary endpoints

First author (year)	Comparison	Number of stents used; Mean (SD)	Procedure time (min); Mean (SD)	HR /RR (95%CI) for Mortality	HR /RR (95%CI) for major adverse cardiac events	HR /RR (95%CI) for myocardial infarction (%)
Pijls (2010)	Angio-guided	2.7 (1.2)	70 (44)	0.67 (0.33–1.34)	0.80 (0.62–1.02)	0.62 (0.40–0.95)
	FFR-guided	1.9 (1.30)	71 (43)			
Koo (2008)	Angio-guided	1.7 (1.1)	NA	NA	NA	NA
	FFR-guided	1.1 (1.2)	NA			
Wongpraparut (2005)	Angio-guided	1.28 (0.92)	88 (30)	NA	NA	NA
	FFR-guided	1.04 (0.49)	91 (37)			
Frohlich (2014)	Angio-guided	1.7 (1.1)	NA	0.88 (0.67–1.16)	NA	NA
	FFR-guided	1.1 (1.2)	NA			
Li (2013)	Angio-guided	1.5 (1.0)	NA	0.89 (0.73–1.10)	1.01 (0.89–1.14)	0.79 (0.58–1.07)
	FFR-guided	0.6 (0.9)	NA			
Di Serafino (2013)	Angio guided	0.7 (0.8)	62 (33)	0.81 (0.39-1.66)	0.47 (0.30-0.75)	0.28 (0.08-0.93)
	FFR guided	0.3 (0.5)	68 (26)			
Puymirat (2012)	Angio-guided	1.21 (0.63)	NA	0.684 (0.355–1.316)	0.458 (0.310–0.679)	0.063 (0.009–0.462)
	FFR-guided	0.45 (0.73)	NA			

Abbreviations: PCI = percutaneous coronary intervention; FFR = fractional flow reserve; Angio = angiography; and, NA = not available.

FIGURE 1. Flow diagram of study selection (A), risk-of-bias summary for individual (B) and percentages of biases of all included studies (C).

FIGURE 2. Meta-analysis (A) and sensitivity analysis (B) for the number of stent used between angiography-guided and FFR-guided PCI groups.

Study characteristics

The seven studies included a total of 49,517 patients, with the number of patients in each study ranging from 137 to 39,857 (Table 1). A total of 4,755 patients underwent FFR, while 44,697 received angiography-guided PCI. The mean age of patients ranged from 58 to 71.7 years. The average number of stents used in FFR patients ranged from 0.3-1.9, and in angiography-guided PCI patients ranged from 0.7-2.7.

Quality assessment

We used the Risk-of-Bias tool, a component of the Cochrane Review Manager, to determine the overall quality of the included randomized-controlled studies. This tool assesses

selection, detection, performance, reporting, and attrition bias as well as evaluates the use of an intent-to-treat population. Figure 1B showed risk-of-bias summary, which is the quality assessment result of individual study. Figure 1C show percentages of biases of all included studies.

Primary outcome: number of stents used

As shown in Figure 2A, a random-effects model of analysis (Q statistic = 81.47, $I^2 = 93.83\%$, $P < 0.001$) revealed there was a greater number of stents placed in the angiography-guided group compared with the FFR group (pooled difference in means: -0.64, 95% CI: -0.81 to -0.47, $P < 0.001$).

A random-effects model was used for the analysis of prospective/RCTs ($Q = 13.07$, $I^2 = 92.31\%$, $P < 0.001$), and

FIGURE 3. Meta-analysis (A) and sensitivity analysis (B) for the procedure time between angiography-guided and FFR-guided PCI groups.

the results indicated that more stents were placed in the angiography-guided group than the FFR group (pooled difference in means: -0.55, 95% CI: -0.86 to -0.24, $P < 0.001$). For non-RCTs a random-effects model analysis ($Q = 68.17$, $I^2 = 95.60\%$, $P < 0.001$) revealed more stents were placed in the angiography-guided group than the FFR group (pooled difference in means: -0.68, 95% CI: -0.88 to -0.48, $P < 0.001$). Sensitivity analysis using the leave-one-out approach revealed the direction and magnitude of combined estimates did not vary markedly with the removal of the studies, indicating good reliability and that the data was not overly influenced by each study (Figure 2B).

Procedure time

Only three studies provided the complete data on procedure time and were included in this analysis. Since there was no evidence of significant heterogeneity when data from the three studies were pooled ($Q = 0.89$, $I^2 = 0\%$, $P = 0.642$), a fixed-effects model of analysis was used (Figure 3A). The analysis showed no significant difference in the procedure time

between FFR- and angiography-guided PCI patients (pooled difference in means: 2.42, 95% CI: -1.85 to 6.69, $P = 0.267$). A fixed-effects model analysis ($Q = 0.10$, $I^2 = 0\%$, $P = 0.753$) was used for the analysis of prospective/RCTs ($n=2$). The analysis showed no significant difference in the procedure time between the FFR- and angiography-guided PCI groups (pooled difference in means: 1.37, 95% CI: -3.48 to 6.22, $P = 0.579$). There was only one non-RCT [19], so no subgroup analysis was performed.

Sensitivity analysis revealed the direction and magnitude of combined estimates did not vary markedly with the removal of the studies, indicating good reliability and that the data was not overly influenced by each study (Figure 3B).

Mortality

As shown in Figure 4A, a fixed-effects model of analysis (Q statistic = 1.12, $I^2 = 0\%$, $P = 0.891$) indicated that FFR-guided PCI patients had a lower mortality rate compared with angiography-guided PCI patients; however, statistical significance was not reached (pooled HR/RR = 0.86, 95% CI: 0.74 to 1.00, $P = 0.050$).

Non RCT

Heterogeneity test: $Q = 0.61$, $df = 3$, $P = 0.894$, $I^2 = 0\%$

Overall

Heterogeneity test: $Q = 1.12$, $df = 4$, $P = 0.891$, $I^2 = 0\%$

FIGURE 4. Meta-analysis (A) and sensitivity analysis (B) for mortality between angiography-guided and FFR-guided PCI groups.

Sensitivity analysis revealed the direction and magnitude of combined estimates did not vary markedly with the removal of the studies, indicating good reliability and that the data was not overly influenced by each study (Figure 4B).

MI rate

As shown in Figure 5A, a random-effects model of analysis (Q statistic = 8.71, $I^2 = 65.56\%$, $P = 0.033$) revealed no significant difference in the MI rate between the FFR- and angiography-guided PCI group (pooled HR/RR = 0.39, 95% CI: 0.13 to 1.16, $P = 0.091$).

Only one study [11] provided the RR for the rate of MI, and it indicated FFR-guided PCI patients were less likely to have a MI compared to angiography-guided PCI patients (HR = 0.62, 95% CI: 0.40 to 0.96, $P = 0.030$). For the subgroup of

non-RCTs, a random-effects model was used for the analysis ($Q = 8.49$, $I^2 = 76.73\%$, $P = 0.014$). The analysis showed no significant difference in the MI rate between FFR- and angiography-guided PCI patients (pooled HR/RR = 0.32, 95% CI: 0.09 to 1.18, $P = 0.087$).

Sensitivity analysis indicated the removal of the study by Li *et al.*, [18] and Puymirat *et al.*, [8] resulted in the pooled HR/RR becoming significant (Figure 5B), indicating that the pooled estimates might be influenced by these two individual studies.

MACE rate

As shown in Figure 6A, a random-effects model of analysis (Q statistic = 23.18, $I^2 = 87.06\%$, $P < 0.001$) revealed no significant difference in the rate of MACE between patients

FIGURE 5. Meta-analysis (A) and sensitivity analysis (B) for myocardial infarction rate between angiography-guided and FFR-guided PCI groups.

the FFR and angiography-guided PCI groups (pooled HR/RR = 0.66, 95% CI: 0.39 to 1.12, $P = 0.125$).

In the subgroup of three non-RCTs, a random-effects model analysis ($Q = 22.47$, $I^2 = 91.10\%$, $P < 0.001$) showed no significant difference in the MACE rate between the FFR and angiography-guided PCI groups (pooled HR/RR = 0.62, 95% CI: 0.31 to 1.14, $P = 0.125$).

Sensitivity analysis indicated that the removal of the study by Li *et al.*, [18] caused the pooled HR/RR to become significant (Figure 6B), indicating that the pooled estimates might be influenced by this study.

Publication Bias

Publication bias analysis was not performed because 10 or more studies are required to detect funnel plot asymmetry [20].

Discussion

In patients with multivessel CAD, the identification of lesions that warrant stenting is difficult [11]. The use of PCI of intermediate stenosis without evidence of ischemia is frequent in clinical practice, but its benefit is highly debated. When revascularization is based mainly on angiographic guidance, a number of hemodynamically non-significant stenoses will be revascularized [21], and revascularization of non-ischemic lesions is controversial [22-24]. A recent analysis in patients

FIGURE 6. Meta-analysis (A) and sensitivity analysis (B) for major adverse cardiac events rate (death, myocardial infarction, and any repeat revascularization) between angiography-guided and FFR-guided PCI groups.

with left main coronary disease comparing revascularization with deferred revascularization, suggested a higher incidence of adverse cardiovascular events in both the groups [1]. In patients with stable CAD and objectively-documented myocardial ischemia, PCI with medical therapy was not associated with a reduction in death, as compared with medical therapy alone [25]. Although coronary angiography often underestimates or overestimates the functional severity of a lesion, it is still the standard technique for guiding PCI in patients with multivessel CAD [26].

Coronary pressure-derived FFR is an invasive index used to identify stenosis responsible for reversible ischemia, and is well validated [21, 27, 28]. An FFR of 0.80 discriminates coronary stenosis responsible for ischemia with an accuracy >90% [29, 30]. The FAME study reported favorable outcomes of FFR-guided PCI when compared with conventional angiography guided PCI [11, 22]. FFR also reduces the need

for revascularization of many of intermediate lesions [31], and is associated with improved health and economic outcomes compared to treatment based on angiography alone [6, 32]. As a result, FFR guidance during PCI has received a class 1A recommendation from the European Society of Cardiology [33], and a class IIA recommendation from the American College of Cardiology [34]; however, FFR is still underutilized clinically with <10% of PCI performed in the absence of clinical evidence of ischemia [35, 36].

The current meta-analysis indicated that FFR-guided PCI offers favorable treatment outcomes over the conventional angiography-guided PCI. Our analysis revealed more stents were placed in the angiography-guided group compared with the FFR group. The overall analysis also indicated that patients with FFR had a lower mortality rate, though the difference between groups did not reach statistical significance. In

addition, the procedure time, MACE rate and MI rate were not different between the FFR and angiography groups.

Our findings are consistent with findings reported by the FAME study [6], where the number of stents used per patient was 2.7 ± 1.2 in the angiography group *vs.* 1.9 ± 1.3 in the FFR-guided PCI group, and the 1-year event rate was 18.3% *vs.* 13.2% in the FFR group. Similar risk reductions of MACE have been observed in patients with unstable angina undergoing FFR-guided PCI, and the number of stents was also reduced without an increase in hospital stay or procedure time [37].

Our meta-analysis included the most recently published data. Our focus was on treatment outcomes (number of stents, mortality and rate of MACE), so that the clinicians can be more assertive in their decision to use FFR and not completely rely upon the angiographic findings that often fail to provide accurate measures of the hemodynamic significance of coronary stenosis. The favourable outcome of an FFR-guided strategy in this study, and studies elsewhere, suggests that FFR should be assessed in patients with intermediate stenosis before a decision is "blindly" made about the need for revascularization [28]. Furthermore, the sensitivity analysis indicated that our meta-analysis had good reliability, as the direction and magnitude of combined estimates did not vary markedly with the removal of the studies, indicating the data was not overly influenced by each included study.

Some of the confounding factors in translating the current results to clinical practice include the bias of the operator in choosing a revascularization strategy, and the imperative that no PCI would be performed if a patient has a non-significant FFR measurement. The functional significance of coronary stenosis will still be the deciding factor in performing PCI in FFR-guided procedures. It has been shown that the use of early angioplasty in patients with FFR <0.75 may not necessarily improve clinical outcomes over 24 months [2]. Similarly, in patients with marked microvascular dysfunction, FFR may not be reliable for the assessment of coronary lesion severity [38].

Although the primary outcome in our study may seem procedural, i.e., the number of stents used, reducing the number of stents used can have clinical implications, considering the practice of over-stenting in multivessel CAD, and the unnecessary cost and risks associated with it. A recently published review by Zhang *et al.* [39], based on similar studies but with different outcomes of interest and a more clinical focus on MACE/MACCE, complements our findings. The FAME study also demonstrated the diminished use of stents in FFR-guided PCI [6]. This analysis, together with the FAME study results, indicates that FFR has a stent-sparing

effect, which, in turn, can significantly reduce the use of hospital resources and cost, as well as stent-related risks. The difference in the number of stents used has important cost implications and this has the potential to influence decisions by policy makers.

There are limitations to this analysis. The number of included studies was relatively small, and three of the seven studies were retrospective. While the results of analysis of retrospective and prospective studies were generally consistent, in some analyses the sensitivity analysis indicated that the results may have been overly influenced by the studies of Li *et al.* [18] and/or Puymirat *et al.* [8]. In addition, only one study used a visual assessment of coronary stenosis, as opposed to quantitative assessment [18].

In conclusion, the current analysis revealed a significantly lower number of stents placed in the FFR-guided PCI group, which reduces both the overall costs and potentially stent-related complications (thromboses and/or restenoses), in comparison with the angiography-guided PCI. No differences in any other outcome measures were noted.

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