Outcomes Associated With Fractional Flow-Guided Revascularization: A Meta-analysis

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ABSTRACT

Background: Deferral of revascularization for abnormal but nonischemic lesions is usually recommended; however, the long-term outcome of this approach is not well known.

Hypothesis: Deferral of nonischemic lesions will be associated with a low frequency of adverse events.

Methods: A PubMed search of the MEDLINE database identified studies that reported clinical outcomes among patients who had fractional flow reserve-guided revascularization. We further categorized studies into 2 subgroups: left main and non-left main coronary artery lesions. Baseline demographics and clinical outcome data were extracted by 3 independent reviewers. Fixed and random effects summary risk ratios were constructed using Mantel-Haenszel and DerSimonian-Laird models, respectively. The primary outcome was the composite of death, myocardial infarction, and revascularization.

Results: From 741 potential studies, 17 were included in the meta-analysis ($n = 2975$ participants), 8 in the left main subgroup ($n = 595$) and 9 studies ($n = 2380$) in non-left main subgroup. In the left main subgroup, the incidence of the composite outcome was 15.3% in the no-ischemia/deferral group vs 14.3% in the ischemia/revascularization group (risk ratio [RR] = 1.13, 95% confidence interval [CI]: 0.76-1.68, $P = 0.54$, $I^2 = 3.7\%$). In the non-left main subgroup, the incidence of the composite outcome was 9.2% in the no-ischemia/deferral group vs 18.8% in the ischemia/revascularization group (RR = 0.42, 95% CI: 0.34-0.52, $P < 0.0001$, $I^2 = 20.7\%$).

Conclusions: Patients with left main coronary disease had a relatively high incidence of adverse cardiovascular events, which was similar in both the deferral and revascularization groups. In patients with non-left main disease, ischemia was associated with worse outcomes despite revascularization.

Introduction

Fractional flow reserve (FFR) is defined as the ratio of maximal achievable blood flow in a coronary artery to the hypothetical maximal achievable blood flow in that same artery in the absence of stenosis. It is derived from the ratio of the mean distal coronary artery pressure to the mean aortic pressure during the period of maximum hyperemia induced by adenosine administration.¹⁻⁵ FFR has been available in cardiac catheterization laboratories to guide the decision making in patients with an intermediate single stenosis, complex bifurcations and ostial branch stenoses, multivessel coronary artery disease, and left main stenosis over the last several decades.^{2,3,5}

Lesions with FFR values below 0.75 are considered ischemia producing, and revascularization of these lesions has been recommended.^{6,7} More recent studies have increased the threshold to 0.80 to increase the test

sensitivity^{8,9}; therefore, the range 0.75 to 0.80 is considered as a “grey-zone” area. Revascularization is usually deferred for nonischemic lesions with FFR values above 0.80.^{1,7,10} Only a few prospective studies have evaluated the long-term outcome of deferral of revascularization in this conservatively managed group, and the sample size of each individual study was generally small.

Accordingly, we sought to perform a comprehensive meta-analysis to evaluate the long-term outcomes from deferral of revascularization in coronary lesions without inducible ischemia in patients with stable coronary artery disease.

Methods

Selection Criteria

We performed a computerized literature search of the MEDLINE database with no language restriction. The last update for the search was January 2014. The search strategy used is shown in Figure 1.

We selected studies that reported clinical outcomes among patients with stable coronary artery disease who

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Figure 1. Study selection flow diagram showing a summary of how the systematic search was conducted and how eligible studies were identified. Abbreviations: ACS, acute coronary syndrome; FFR, fractional flow reserve; MeSH, Medical Subject Headings.

Table 1. Baseline Characteristics, Mean FFR Values, and Duration of Follow-up

First Author	Year	No. of Patients	Age, y	Male, %	DM, %	Smoker, %	Prior MI, %	FFR Value	Follow-up Duration, mo
Left main studies									
Hamilos et al ^{9,a}	2009	136/73	68/64	71/73	20/25	43/52	13/28	0.88/0.73	35
Courtis et al ^{10,b}	2009	82/60	63/61	78/44	26/33	21/30	26/22	0.88/0.73	14
Linstaedt et al ^{23,b}	2006	24/27	64/61	83/77	33/44	50/59	29/37	0.90/0.70	29
Suemaru et al ²⁷	2005	08/07	65/70	88/100	88/71	13/14	NR	0.91/0.61	33
Legutko et al ²²	2005	20/18	56/53	80/72	10/11	45/50	30/50	0.84/0.66	24
Jasti et al ¹⁹	2004	41/13	62/62	NR	32/32	63/63	NR	0.91/0.67	38
Jimenez-Navarro et al ²⁰	2004	20/07	64/60	75/86	20/42	60/57	50/42	0.88/0.68	26
Bech et al ⁶	2001	24/30	60/63	75/87	33/20	29/63	33/16	0.90/0.67	29
Non-left main studies									
FAME II ^{8,a}	2012	166/447	64/64	68/80	25/27	20/21	37/37	NR/0.68	8
Muller et al ^{25,a}	2011	564/166	69/67	55/76	17/19	35/46	NR	0.87/0.71	38
Misaka et al ²⁴	2011	29/15	66/65	76/87	52/33	48/40	NR	0.86/0.64	53
DEFER ²⁶	2007	91/144	61/60	65/80	15/13	27/29	NR	0.87/0.56	60
PHANTOM ¹⁷	2007	39/21	62/62	70/70	40/40	17/17	NR	0.87/0.64	12
Hirota et al ¹⁸	2006	26/46	65/67	85/85	58/42	73/49	NR	0.83/0.59	18

Table 1. Continued

First Author	Year	No. of Patients	Age, y	Male, %	DM, %	Smoker, %	Prior MI, %	FFR Value	Follow-up Duration, mo
Verna et al ²⁸	2006	54/58	61/65	69/79	11/08	24/34	44/58	NR	34
Legalery et al ^{21,a}	2005	237/99	60/58	69/67	25/24	59/66	NR	0.88/0.75	12
Rieber et al ²⁹	2002	59/48	65/65	73/73	15/15	8/15	41/44	0.90/0.66	12

Abbreviations: DEFER, Deferral Versus Performance of PTCA in Patients Without Documented Ischemia; DM, diabetes mellitus; FAME II, Fractional Flow Reserve Versus Angiography for Multivessel Evaluation II; FFR, fractional flow reserve; MI, myocardial infarction; NR, not reported; PHANTOM, Physiologic and Anatomical Evaluation Prior To and After Stent Implantation in Small Coronary Vessels.
Data are formatted as deferral group/revascularization group
^aStudies that used FFR value of 0.80 as the threshold for ischemia. ^b Studies that deferred revascularization for FFR >0.80, performed revascularization for FFR <0.75, and individualized treatment for FFR 0.75 to 0.79.

Table 2. Study Design, Primary Outcome of the Study, and the Completeness of Follow-up

First Author	Study Design	Study Primary Outcome	Completeness of Follow-up (%)
Left main studies			
Hamilos et al ⁹	Prospective, single center	Composite of death, MI, revascularization	98
Courtis et al ¹⁰	Prospective, single center	Composite of death, MI, revascularization	100
Linstaedt et al ²³	Prospective, single center	Composite of death, MI, revascularization	100
Suamaru et al ²⁷	Prospective, single center	Composite of CV death, MI, hospitalization for angina	100
Legutko et al ²²	Prospective, single center	Composite of death, MI, revascularization	100
Jasti et al ¹⁹	Prospective, single center	Composite of death, MI, revascularization	100
Jimenez-Navarro et al ²⁰	Prospective, single center	Composite of death, MI, revascularization	100
Bech et al ⁶	Prospective, multicenter	Composite of death, MI, revascularization	100
Non-left main studies			
FAME II ⁸	Randomized, prospective, multicenter	Composite of death, MI, revascularization	99
Muller et al ²⁵	Prospective, single center	Composite of death, MI, revascularization	100
Misaka et al ²⁴	Prospective, single center	Composite of death, MI, revascularization	100
DEFER ²⁶	Randomized, prospective, multicenter	Composite of death, MI, revascularization	98
PHANTOM ¹⁷	Prospective, multicenter	CV death, MI, revascularization	100
Hirota et al ¹⁸	Prospective, single center	CV death, MI, TVR	100
Verna et al ²⁸	Prospective, single center	Composite of death, MI, revascularization	100
Legalery et al ²¹	Prospective, single center	Composite of death, MI, revascularization	99
Rieber et al ²⁹	Prospective, single center	Composite of death, MI, revascularization	96

Abbreviations: CV, cardiovascular; DEFER, Deferral Versus Performance of PTCA in Patients Without Documented Ischemia; FAME II, Fractional Flow Reserve Versus Angiography for Multivessel Evaluation II; MI, myocardial infarction; PHANTOM, Physiologic and Anatomical Evaluation Prior To and After Stent Implantation in Small Coronary Vessels; TVR, target vessel revascularization.

had FFR-guided revascularization. We required that studies defined a threshold FFR value for myocardial ischemia. Accordingly, there were 2 groups, the no-ischemia/deferral group and the ischemia/revascularization group. Revascularization could be performed either by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) depending on the coronary anatomy and operator discretion. We excluded studies that did not report clinical outcome data and studies that compared revascularization

vs medical management within the same FFR range. We classified patient subgroups according to the affected coronary artery: left main vs non-left main coronary artery disease.

Outcomes and Definitions

The primary outcome was the composite of death, nonfatal myocardial infarction (MI), and revascularization. Secondary outcomes included all-cause mortality,

Figure 2. Summary plot for the composite outcome. The plot compares the relative safety of deferring revascularization of nonischemic lesions compared with performing revascularization of ischemic lesions. The relative size of the data markers indicates the weight of the sample size from each study. Abbreviations: CI, confidence interval; DEFER, Deferral Versus Performance of PTCA in Patients Without Documented Ischemia; FAME II, Fractional Flow Reserve Versus Angiography for Multivessel Evaluation II; RR, risk ratio; PHANTOM, Physiologic and Anatomical Evaluation Prior To and After Stent Implantation in Small Coronary Vessels.

Figure 3. Summary plot for all-cause mortality. The relative size of the data markers indicates the weight of the sample size from each study. Abbreviations: CI, confidence interval; DEFER, Deferral Versus Performance of PTCA in Patients Without Documented Ischemia; FAME II, Fractional Flow Reserve Versus Angiography for Multivessel Evaluation II; PHANTOM, Physiologic and Anatomical Evaluation Prior To and After Stent Implantation in Small Coronary Vessels; RR, risk ratio.

Figure 4. Summary plot for myocardial infarction. The relative size of the data markers indicates the weight of the sample size from each study. Abbreviations: CI, confidence interval; DEFER, Deferral Versus Performance of PTCA in Patients Without Documented Ischemia; FAME II, Fractional Flow Reserve Versus Angiography for Multivessel Evaluation II; PHANTOM, Physiologic and Anatomical Evaluation Prior To and After Stent Implantation in Small Coronary Vessels; RR, risk ratio.

cardiovascular mortality, non-fatal MI, total revascularization, target vessel revascularization, and non-target vessel revascularization separately.

Cardiovascular mortality was defined as any death due to an immediate cardiac cause. MI was defined as ischemic symptoms, plus an elevation in cardiac markers or appearance of new Q waves in 2 consecutive leads on a 12-lead electrocardiogram. Revascularization was defined as ischemic symptoms that resulted in a revascularization procedure (either PCI or CABG). Revascularization was further defined in reference to the target segment.

Data Extraction

Data were independently extracted by the 3 authors (A.A.B., I.Y.E., and J.W.P.). Any discrepancies were resolved by consensus of the authors. Baseline patient characteristics were extracted as well as data about FFR values, mode of treatment, and duration of follow-up. For all clinical outcomes, we tabulated the number of events that occurred in each arm of each study. For non-English articles, we used Google Translator (Google, Inc., Mountain View, CA).

Statistical Analysis

We analyzed outcomes by the intention-to-treat method. We used a Mantel-Haenszel model to construct fixed-effects

summary risk ratios (RRs)¹¹ and a DerSimonian-Laird model to construct random-effects summary RRs.¹² We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for conducting a high-quality meta-analysis.¹³ We quantified statistical heterogeneity for each outcome of interest by using the I^2 statistic. I^2 statistic values <25%, 25% to 50%, and >50% were considered as low, moderate, and high degree of heterogeneity, respectively.¹⁴ Publication bias was assessed by using Egger's and Begg's tests.^{15,16} P values were set at a statistical significance level of 0.05, and confidence intervals (CIs) were calculated at the 95% level. All analyses were performed using Stata software version 11 (StataCorp, College Station, TX).

Results

Baseline Characteristics

Overall, there were 17 studies with 2975 patients available for analysis.^{7–10,17–29} The left main coronary artery disease subgroup included 8 studies, including 357 in the no ischemia/deferral group and 238 in the ischemia/revascularization group.^{7,9,10,19,20,22,23,27} The non-left main coronary artery disease subgroup included 9 studies, including 1299 in the no ischemia/deferral group and 1081 in the ischemia/revascularization group.^{17,18,21,24–26,28,29}

Figure 5. Summary plot for revascularization. The relative size of the data markers indicates the weight of the sample size from each study. Abbreviations: CI, confidence interval; DEFER, Deferral Versus Performance of PTCA in Patients Without Documented Ischemia; FAME II, Fractional Flow Reserve Versus Angiography for Multivessel Evaluation II; PHANTOM, Physiologic and Anatomical Evaluation Prior To and After Stent Implantation in Small Coronary Vessels; RR, risk ratio.

In the left main subgroup, the mean age in the no ischemia/deferral group was 63 (± 3) years and 62 (± 5) years in the ischemia/revascularization group, whereas the mean FFR was 0.89 vs 0.68, respectively. In the non-left main subgroup, the mean age was 64 (± 3) years in both the deferral/no ischemia and the ischemia/revascularization groups, whereas the mean FFR was 0.87 vs 0.65, respectively. The mean follow-up duration was 29 (± 7) months in the left main subgroup and 30 (± 22) months in non-left main subgroup. In the left main subgroup, the majority of the patients with ischemia producing lesions were treated with CABG, except in 1 study in which half of the participants were treated by CABG and the other half by PCI.¹⁹

Complete baseline characteristics, mean FFR values, and follow-up duration are reported in Table 1, whereas Table 2 reports the study design, primary outcome of the study, and the completeness of follow-up.

Outcomes in the Left Main Subgroup

The incidence of the composite of death, MI, and revascularization was 15.3% in the no-ischemia/deferral group vs 14.3% in the ischemia/revascularization group (fixed effects model: RR = 1.13, 95% CI: 0.76-1.68, $P=0.54$, $I^2=3.7\%$; random effects model: RR=1.07, 95% CI:

0.70-1.64, $P=0.75$, $I^2=3.7\%$), with no evidence of publication bias with Begg's test ($P=0.85$) or Egger's test ($P=0.76$) (Figure 2A). The incidence of all-cause mortality was 4.8% in the no-ischemia/deferral group vs 8.1% in the ischemia/revascularization group (random effects model: RR=0.57, 95% CI: 0.30-1.10, $P=0.09$, $I^2=0\%$) (Figure 3A). The incidence of MI was comparable in the no-ischemia/deferral group at 1.7% vs 1.7% in the ischemia/revascularization group (random-effects model: RR=1.21, 95% CI: 0.34-4.30, $P=0.76$, $I^2=0\%$) (Figure 4A). The incidence of revascularization was 12.5% in the no-ischemia/deferral group vs 3% in the ischemia/revascularization group (random-effects model: RR=3.17, 95% CI: 1.57-6.41, $P=0.001$, $I^2=0\%$) (Figure 5A).

Outcomes in the Non-Left Main Subgroup

The incidence of the composite outcome in the non-left main group was 9.2% in the no-ischemia/deferral group vs 18.8% in the ischemia/revascularization group (fixed-effects model: RR=0.42, 95% CI: 0.34-0.52, $P<0.0001$, $I^2=20.7\%$; random-effects model: RR=0.43, 95% CI: 0.32-0.56, $P<0.0001$, $I^2=20.7\%$), with no evidence of publication bias with Begg's test ($P=0.92$) or Egger's test ($P=0.65$) (Figure 2B). The incidence of all-cause mortality was 3.2% in the no-ischemia/deferral group vs 3.7% in the

ischemia/revascularization group (random-effects model: RR = 0.58, 95% CI: 0.36-0.92, $P = 0.02$, $I^2 = 0\%$) (Figure 3B). The incidence of MI was 0.7% in the no-ischemia/deferral group vs 3.3% in the ischemia/revascularization group (random-effects model: RR = 0.43, 95% CI: 0.19-0.98, $P = 0.05$, $I^2 = 0\%$) (Figure 4B). The incidence of revascularization was 4.2% in the no-ischemia/deferral group vs 12% in the ischemia/revascularization group (random-effects model: RR = 0.38, 95% CI: 0.22-0.66, $P = 0.001$, $I^2 = 59.1\%$) (Figure 5B).

Table 3 reports fixed and random-effects models for the composite outcome, all-cause mortality, cardiovascular mortality, noncardiovascular mortality, MI, and revascularization, including target vessel and non-target vessel revascularization.

Discussion

In this study, we analyzed 17 studies that included 2975 patients with stable coronary artery disease. Our analysis showed that patients with left main coronary lesions tend to have a higher incidence of major adverse cardiovascular events compared with non-left main lesions. Moreover, the high incidence of adverse events was similar irrespective of the lesion being ischemic or nonischemic as determined by FFR. This indicates that borderline left main coronary stenosis, whether flow limiting or not, portends poor prognosis. However, in the non-left main subgroup, the ischemia/revascularization group tended to have worse outcomes when compared to the no ischemia/deferral group. This finding is likely explained by the higher burden of atherosclerotic disease in patients with myocardial ischemia compared to those without myocardial ischemia. Although revascularization is effective at controlling angina symptoms, the higher burden of underlying atherosclerosis likely drove the occurrence of future adverse events. It is important to note that this study compared 2 different types of coronary disease patterns (myocardial ischemia vs no myocardial ischemia) and did not compare revascularization vs conservative therapy.

It is worth noting that the optimal treatment strategy for patients above and below the FFR cutoff was not clearly addressed by most of the published studies evaluating the application of FFR. Although our study demonstrates that adverse outcomes were comparable with deferral of PCI for nonischemic lesions, as compared to revascularization of ischemia-producing lesions, our study did not specifically compare strategies within a certain FFR range.

There are some limitations to this study. First, as most meta-analyses, we had no access to the primary data. Second, the threshold for ischemia was not uniformly defined among the studies, as some studies used the cutoff 0.75 and others used 0.8, but from the available data we know that the FFR threshold for ischemia lies somewhere between 0.75 and 0.80. Third, most of the included studies were of small sample size, though the argument can be made that including these studies would reduce the potential publication bias.³⁰ Fourth, this meta-analysis mostly predates current interventional practice with drug-eluting stents, which might have helped to reduce adverse events among the non-left main group

Table 3. Fixed and Random Effect Models Comparing the Primary and Secondary Outcomes in the No Ischemia/Deferral Group to the Ischemia/Revascularization Group

Outcome	Model	RR	95% CI	P Value	I^2 %
Left main studies					
Composite outcome	Fixed effect	1.13	0.76-1.68	0.54	3.7
	Random effect	1.07	0.70-1.64	0.75	3.7
All-cause mortality	Fixed effect	0.55	0.29-1.03	0.06	0
	Random effect	0.57	0.30-1.10	0.09	0
CV mortality	Fixed effect	0.49	0.14-1.69	0.26	0
	Random effect	0.55	0.14-2.11	0.38	0
Non-CV mortality	Fixed effect	0.50	0.17-1.45	0.20	0
	Random effect	0.44	0.14-1.40	0.17	0
MI	Fixed effect	1.15	0.38-3.48	0.80	0
	Random effect	1.21	0.34-4.30	0.76	0
Revascularization	Fixed effect	3.55	1.78-7.08	<0.0001	0
	Random effect	3.17	1.57-6.41	0.001	0
TVR	Fixed effect	3.38	1.26-9.05	0.02	0
	Random effect	2.67	0.96-7.43	0.06	0
Non-TVR	Fixed effect	2.66	1.18-5.96	0.02	0
	Random effect	2.48	1.07-5.76	0.03	0
Non-left main studies					
Composite outcome	Fixed effect	0.42	0.34-0.52	<0.0001	20.7
	Random effect	0.43	0.32-0.56	<0.0001	20.7
All-cause mortality	Fixed effect	0.55	0.35-0.86	0.01	0
	Random effect	0.58	0.36-0.92	0.02	0
CV mortality	Fixed effect	0.43	0.15-1.25	0.12	0
	Random effect	0.47	0.16-1.44	0.12	0
Non-CV mortality	Fixed effect	0.57	0.17-1.87	0.35	47.8
	Random	0.51	0.06-4.46	0.55	47.8
MI	Fixed effect	0.35	0.16-0.75	0.01	0
	Random effect	0.43	0.19-0.98	0.05	0
Revascularization	Fixed effect	0.38	0.28-0.51	<0.0001	59.1
	Random effect	0.38	0.22-0.66	0.001	59.1
TVR	Fixed effect	0.41	0.26-0.67	<0.0001	0
	Random effect	0.43	0.26-0.70	0.001	0

Abbreviations: CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; RR, risk ratio; TVR, target vessel revascularization.

that underwent revascularization.³¹ Medical therapy has also evolved to include potent adenosine diphosphate antagonists and potent statin therapy.

Conclusion

Borderline left main coronary stenosis portends a poor prognosis. Although adverse cardiovascular events are similar between ischemic and nonischemic left main lesions, the need for future revascularization is greater among those who initially had no ischemia/deferral of revascularization. Among the non-left main subgroup, ischemic patients had a higher event rate than nonischemic patients, despite being revascularized.

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