Comparison of Outcomes between Fractional-Flow-Reserve- and Angiography-Directed Intervention in Non-ST Elevation Acute Coronary Syndrome

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ABSTRACT

Among the sick patients suffering from non-ST segment elevation acute coronary syndrome (NSTEACS), the accuracy of fractional flow reserve (FFR)-directed percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is still ambiguous. Studies were obtained from PubMed, Embase, Wanfang Data, and Cochrane Library electronic statistics from their initiation up to April 2018, to explore the differences between the FFR-directed approach and the coronary angiography (CA)/stress perfusion scintigraphy (SPS)-directed approach in the outcomes of NSTACS patients. Odds ratio was determined for individual studies, quality assessments, heterogeneity, and publishing bias analyses. In total, there were 5 studies involving 1,366 patients (606 FFR patients and 760 CA patients). Compared with CA, the collection of the studies indicated that FFR had a lower incidence of myocardial infarction (MI) (OR, 0.61; 95% CI: 0.39-0.96; p <0.05). However, none showed important disparities in main adverse cardiovascular events (MACE, OR, 0.74; 95% CI: 0.53-1.03; p=0.07), all-cause death rate (OR, 0.83; 95% CI: 0.45-1.54; p = 0.56), and major bleeding (OR, 1.00; 95%CI: 0.25-4.03; p=1). The FFR-directed management of patients with NSTEACS had a close relationship with the serious decrease in incidence of MI without statistical significance. Future large-scale research, which is carried out at random and with a control, is needed to confirm these conclusions.

Key Words: *Acute coronary syndrome (ACS), Fractional flow reserve (FFR), Meta, Myocardial infarction (MI).*

INTRODUCTION

There is still controversy about the application of fractional flow reserve (FFR) to non-ST elevation acute coronary syndromes (ACS) because the benefits of FFR are not clear. In patients with non-ST segment elevation acute coronary syndrome (NSTEACS), the degree of coronary stenosis usually determines the choice of treatment options; and coronary angiography is used to assess the condition.[1] However, the degree of coronary stenosis cannot be accurately evaluated with a subjective assessment of the lesion using coronary angiography to decide whether PCI or CABG would be the most effective choice.[2,3] Subjective assessment of the lesion may be occurring in patients with ACS, involving unstable angina (UA), and non-ST segment elevation myocardial infarction (NSTEMI). We found that FFR is closely associated with cardiac ischemia and FFR showed an extremely positive correlation with the degree of coronary stenosis; therefore, FFR can be applied to assess the capability of affected coronary blood flow.[2,4-6] The meta-reasoning was carried out in order to find the discrepancies between FFR-directed and CA/SPSR-directed approaches in the outcomes of patients with NSTACS.

METHODOLOGY

The meta-reasoning was carried out by applying the Preferred Reporting Items for Systematic Reviews and Meta-reasoning (PRISMA) statement under the guidance.[7] Two investigators (J.J.Y. and X.H.P.) methodically retrieved studies from databases-PubMed, Embase, Wanfang Data, and the Cochrane Central Registry of Controlled Trials from their inception up to April 2018 – with no language limitations. Medical subject heading terms and important words applied included: "unstable angina or UA," "non-ST elevated myocardial infarction or NSTEMI," "acute coronary syndrome or ACS," and "Fractional flow reserve or FFR."

The authors examined controlled experiments of NSTACS patients (including NSTEMI, and UA cases) in which FFR-directed revascularisation was applied in contrast to CA-SPS-directed revascularisation. Standard inclusion research options included control tests carried out in people who suffer from ACS with ongoing ischemic signs and the sick patients who were anticipated to have CA, with coronary artery stenosis accounting for more than 30%, and with an interference of FFR in contrast to CA-SPS-directed revascularisation. We removed the studies that referred to the sick patients

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showing steady coronary artery disease (CAD) and Non-ST elevated myocardial infarction (NSTEMI) studies that were carried out without control, and studies that had no record of the long-term outcomes. In view of the study results, we had no restrictions on eligibility.

Two researchers (Pang X.H, and Yang J.J) independently extracted the following data from each study: the name of the primary writer, the arrangement of the research, research place, the case scale, the basic features of the research, the ratio of PCI sick patients, and the period of the after-trials. All divergences were resolved by discussion with a third investigator (Wang H.L). Results of the assessment consist of death and all-cause death rate, MI, main adverse cardiovascular events (MACE; cardiac death or unexpected hospitalisation for MI or heart failure), and index hospitalisation extended. Major bleeding was reported in these two studies.[6,8]

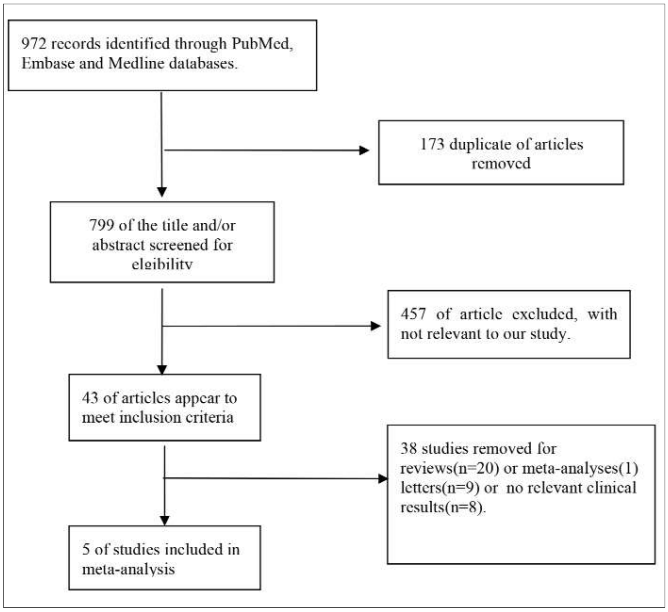

Figure 1: Search strategy conducted for all the included trials. MeSH = Medical subject headings.

The single adventure of bias in each study was assessed by applying the Cochrane adventure of bias estimation device.[9] Data reasoning was based upon the PRISMA statement and the Cochrane Collaboration. Review Manager (RevMan) 5.1 was used to perform the meta-analyses. Heterogeneity between the studies was assessed using I2 statistics of inconsistency and Chi-square test of heterogeneity. I^2 values of 75%, 50%, and 25% indicated as, respectively, high, medium, and low heterogeneity.[10] The Mantel-Haenszel method was applied to compute the summary estimate of odd risks (ORs) with their 95% confidence intervals (CIs). Reported values are two-tailed, and the results of hypothesis testing were deemed statistically different at $p < 0.05$. Funnel plots, Egger's test, and Begg's log-rank testing were applied to test small sample studies, including publication bias.

RESULTS

In total, 969 articles were acquired from the Embase, PubMed, Cochrane, and Wanfang Data databases. After abortive verification, 396 copies were excluded. Of the remaining 573 articles, 530 articles were excluded because they did not pertain to the topic. The remaining 43 full-text articles were assessed as qualified, with 38 articles excluded in that they belonged to meta-analyses, review, or letters to proofreaders; no relevant clinical results were recorded on the clinical endpoints (Figure 1).[6,8,11-13]

In total, there were five reflective researches included, with a total of 1366 ACS patients (consisting of 606 cases in the FFR group and 760 cases in the CA group) identified in this meta-analysis. The median age of the patients in the study was 62.1 years; the median

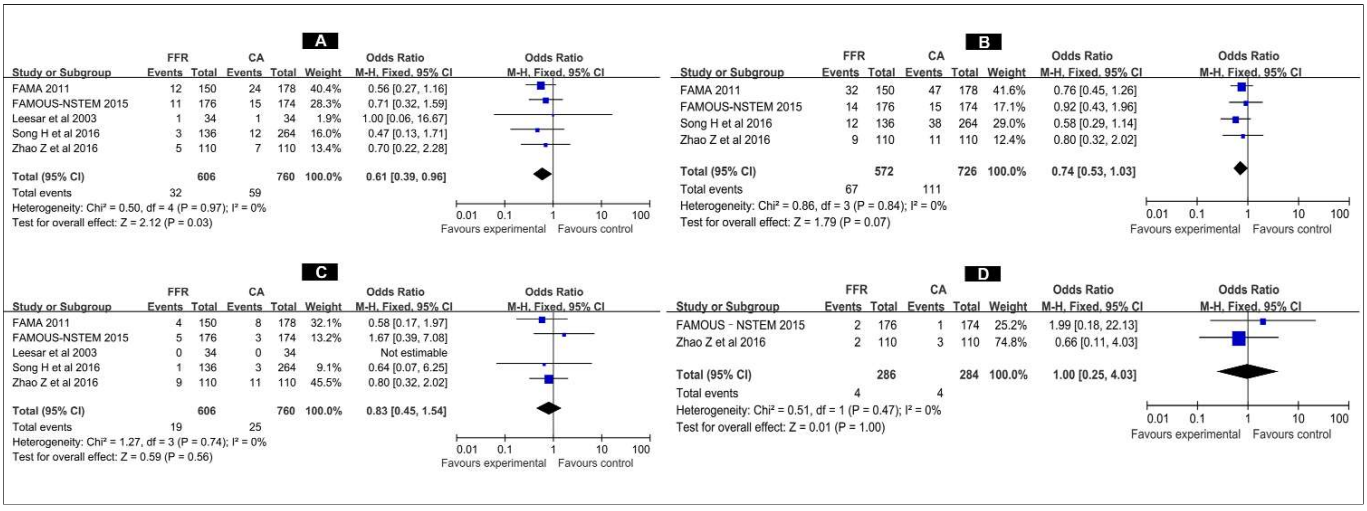

Figure 2: (A) Fixed-effect meta-analysis for myocardial infarction. The figure presents the number of events, the number of patients in the treatment and control groups, the odds ratio (OR) and 95% confidence interval (CI) for each trial, the overall OR estimate with 95% CI and the p-value for the association test, the p-value for the heterogeneity test, and between-trial inconsistency (I2) measures. **(B)** Fixed-effect meta-analysis for MACE. **(C)** Fixed-effect meta-analysis for all-cause mortality. **(D)** Fixed-effect meta-analysis for major bleeding.

age of the CA-directed revascularization group was 61.0 years and the moderate age of the FFR-directed revascularization group was 63.5 years. The characteristics of the baseline in the studies are presented in Table I, and features of the patients in every trial are presented in Table II. All five articles included in the current meta-analysis were from different study groups and different countries. The diagnostic criteria for

Table I: Baseline characteristics of randomised studies.

Randomised studies (year)	Sample size		Inclusion criteria	Exclusion criteria	Endpoints	Mean follow-up period (months)
	Intervention (FFR-directed approach)	Control (CA- or SPS-directed approach)				
Zhao Z; Ke L (2016)	110	110	Patients with NSTEMI who are older than 65 years of age with acute ischemic symptoms and abnormal myocardial markers, but without ST-segment elevation on the electrocardiogram.	Ongoing ischemic symptoms after medical therapy; cardiogenic shock or hemodynamic instability; intolerance to antiplatelet drugs; ineligible for PCI; CAD<30% severity; highly tortuous or calcified coronary arteries; noncoronary cardiosurgery; and life expectancy <1 year.	Adverse events, including major adverse cardiovascular events defined as cardiovascular death, non-fatal myocardial infarction, or unplanned hospitalisation for heart failure, major adverse cardiovascular and cerebrovascular events defined as cardiovascular death, non-fatal myocardial infarction, unplanned hospitalisation for stroke, or transient ischemic attack, all-cause mortality, contrast nephropathy, and major bleeding, and therapeutic strategies (PCI or medical therapy alone).	12
FAMOUS-NSTEMI (2015)	176	174	Patients with a clinical diagnosis of recent NSTEMI and with at least one risk factor for coronary artery disease, with planned invasive management within 72 h of the index episode of event or history of recurrent ischemic symptoms within 5 days of NSTEMI. At least one coronary stenosis $\geq$30% severity with normal coronary blood flow. Thrombolysis in myocardial infarction (TIMI) grade III in which FFR measurement might have a diagnostic value.	Presence of ischemic symptoms that were not controlled by medical therapy, hemodynamic instability, MI with persistent ST elevation, intolerance to anti-platelet drugs, ineligible for coronary revascularisation, a treatment plan for non-coronary heart surgery (e.g., valve surgery), a history of prior CABG, angiographic evidence of severe (e.g., diffuse calcification) or mild (30% severity) coronary disease, and a life expectancy of 1 year.	Between-group difference in the proportion of patients allocated to medical management. The feasibility and safety of routine FFR measurement. The relationship between FFR and coronary stenosis severity by visual assessment of the angiogram. MACE defined as cardiac death or hospitalisation for myocardial infarction or heart failure after randomisation. Cardiovascular death, stroke, transient ischemic attack, contrast nephropathy, and bleeding were also prospectively recorded. Index hospitalisation resource used including: material, procedure, hospitalisation, and in-hospital event costs. Health-related quality of life.	12
FAME (2011)	150	178	Patients with multivessel CAD undergoing PCI by stenting with drug-eluting stents, UA (with or without transient ST-segment changes) and NSTEMI with positive troponin but total creatine kinase of <1000 U/l.	Left main disease, previous CABG, and STEMI 5 days before.	MACE defined as composite of death from any cause, MI, any repeat revascularisation, and their individual components.	24
Leesar *et al.* (2003)	35	35	An episode of angina lasting >20 min or recurrent episodes of angina while at rest and had at least one of the following: a new finding of ST-segment depression; transient (<20 min) ST-segment elevation; a new finding of T-wave inversion in at least two leads; elevated levels of cardiac markers; a history of MI, including a Q-wave on the electrocardiogram or previous admission with a diagnosis of MI; and evidence of prior CAD or history of PCI.	Incessant chest pain that does not respond to medical therapy; left main or multivessel CAD; prior CABG; vessels that were totally occluded or supplying an akinetic territory by visual assessment of the left ventricular angiogram.	Death, MI, CABG, PCI, and readmission because of UA.	13
Song H; Li H (2016)	136	264	Non-ST elevation acute coronary syndromes (NSTEACS), NSTEACS patients who had moderate coronary lesions; Double antiplatelet therapy for at least 1 year.	Patients with hemodynamically unstable or hyperacute period of acute myocardial infarction.	Major adverse cardiac events (MACE), death, non-fatal myocardial infarction (MI), target vessel revascularisation (TVR), and procedure costs.	10

CAD = Coronary artery disease; MI = Myocardial infarction; PCI = Percutaneous coronary intervention; CABG = Coronary artery bypass grafting; UA = Unstable angina.

Table II: Patient characteristics in each randomised trial.

Demographics	Zhao Z; Ke L		FAMOUS-NSTEMI		FAME		Leesar *et al.*		Song H; Li H	
	FFR-directed (110)	CA-directed (110)	FFR-directed (176)	CA-directed (174)	FFR-directed (150)	CA-directed (178)	FFR-directed (35)	CA-directed (35)	FFR-directed (142)	CA-directed (284)
Age, mean	70 ±3.7	70 ±3.4	62.3 ±11	61.6 ±11.1	65.6 ±10	64.2 ±10.5	59 ±6	55 ±4	58.75 ±9.86	55.76 ±9.63
Sex, male (n)	75	78	133	127	110	116	24	22	105	225
Smoking history (n)	70	69	127	118	43	55	20	15	69	150
Prior CAD (n)	24	23	22	22	66	78	9	14	-	-
Hypertension (n)	81	83	78	81	90	122	25	26	89	197
Diabetes mellitus (n)	40	36	26	26	33	38	13	11	39	72
Hyperlipidemia (n)	90	93	71	56	101	129	19	22	25	51
PCI / CABG	95	104	136	151	20	25	2	1	52	133
MI (n)	5	7	11	15	12	24	1	1	3	12
MACE (n)	9	11	14	15	32	47	NA	NA	12	38
Death (n)	9	11	5	3	4	8	0	0	1	3
Major bleeding (n)	2	3	2	1	NA	NA	NA	NA	NA	NA

NA = Not available

Table III: Quality evaluation of the included studies.

Studies	Sample-size calculation	Inclusion and exclusion criteria	Randomisation	Allocation concealment	Blinded assessment of outcomes	Reporting potential conflicts of interest and study funding
Leesar *et al*. (2003)	No	Yes	Yes	No	No	No
FAMA (2011)	No	Yes	Yes	No	No	Yes
FAMOUS-NSTEM (2015)	Yes	Yes	Yes	Yes	Yes	Yes
Song H *et al.* (2016)	No	Yes	No	No	No	Yes
Zhao Z *et al.* (2016)	No	Yes	Yes	No	No	No

coronary artery disease, as well as the cut-off thresholds for FFR and CA, might be different.

Table III lists the quality estimation for each included study. As we can see in this chart, five studies in this meta-analysis reported inclusion and exclusion criteria, four reported randomisation, two reported that there was no potential conflict of interest and listed their sources of financial support; one of the studies described the calculation of sample size, allocation of hidden elements, and blind evaluation of the results in detail. Because five published studies met the inclusion criteria and the information in these studies was less comprehensive than in other studies, the overall quality of these works in the meta-analysis was moderate.

The frequency of MI during the after-trial process was 5.3% for the group of the sick patients who received FFR-directed treatment *versus* 7.8% for the CA/SPS-directed treatment. Compared with CA-directed revascularization, FFR-directed revascularisation had a close relationship with a significant decrease of frequency of MI (OR: 0.61, 95%CI: 0.39-0.96; p <0.05; I2=0%). Due to low heterogeneity, the fixed-effect model was used to calculate the statistics. Egger's and Begg's tests were used to estimate publication bias (Figure 2A).

The frequency of MACE was 11.7% in sick patients with FFR-directed treatment *versus* 15.2% in the CA/SPS-directed treatment. There were no significant differences in the case of MACE (OR: 0.74, 95% CI: 0.53-1.03; p=0.07; I2 = 0%) between two groups (Figure 2B).

The frequency of all-cause death rate was 3.1% in sick patients who received FFR-directed treatment *versus* 3.3% in patients who received CA/SPS-directed treatment. No important discrepancy existed between these two groups in the frequency of all-cause death rate (OR: 0.83, 95% CI: 0.45-1.54; p = 0.56; I2 = 0%) without important heterogeneity in the tests (Figure 2C).

The frequency of major bleeding was 1.3% in sick patients who received FFR-directed treatment competing against 1.4% in the sick patients who received CA/SPS-directed treatment. No important discrepancy existed between these groups in the incidence of major bleeding (OR: 1.00, 95%CI: 0.25-4.03; p = 1.00; I2 = 0%) with no significant heterogeneity in the trials (Figure 2D).

Begg's funnel plot was used to determine whether our conclusions were affected by any publication bias. The results showed no obvious asymmetry for fractional flow reserve-directed management of acute coronary syndromes, indicating that the conclusion of this meta-analysis was not influenced by publication bias.

DISCUSSION

Egger's tests were of no importance for the outcomes of the studies, and the funnel plot displayed symmetry that is in line with publication bias. The meta-reasoning disclosed that the FFR-directed treatment of NSTEACS patients was related to an important decrease of incidence of MI during the process of after-trials and that the FFR-directed treatment of NSTEACS patients no

correlated with decrease in the incidence of MACE. Although the heterogeneity was low, the FFR-directed management of NSTEACS patients had a significant trend in reducing MI. There were no statistical significances in the incidence of MACE, all-cause death rate and major bleeding between the FFR-directed treatment group and the CA/SPS-directed treatment group, but our meta-analysis showed that the FFR-directed treatment of ACS patients was still not related to modest reduction in incidence of MACE during the follow-up period.

In a wide range of studies, FFR had been used to determine the practical importance of moderate coronary artery stenosis.[14,15] For NSTEACS sick patients, who have moderate coronary stenosis, FFR-directed therapy was found to further decrease the incidence of myocardial infarction than the assessment of coronary angiographic.[16,17] In NSTEACS patients with moderate coronary stenosis, the revascularisation programme is based upon the severity of the anatomical assessment of the coronary artery, rather than a functional assessment. Based on the earlier meta-reasoning by Briasoulis and his coworkers, their studies displayed no important difference between the FFR-directed management of NSTEACS patients and the CA-directed management of NSTEACS patients in reducing the incidence of MI. Our study found that there is an important discrepancy between the two groups in reducing the incidence of MI. FFR-directed revascularisation can greatly reduce the frequency of MI in sick patients with NSTEACS, and this trend was more obvious after increasing the data from the studies.[18] In addition, large trials may be able to prove these outcomes in the future, then the decrease of MACE related to FFR-directed revascularisation will probably be more obvious. FFR helped to more accurately guide the need for PCI or CABG in the NSTEACS patients. During the acute stage of acute coronary syndromes, the seriousness of the coronary artery stenoses can be estimated accurately by FFR. This provides a decision about the demand for additional revascularisation to be made that might be beneficial to better risk stratification. In these studies, the presence of CAD was defined by the visual assessment of the stenosis. However, the accurate judgment of the hemodynamic seriousness of the coronary artery stenoses with fractional flow reserve (FFR) during the acute stage of an NSTEACS can enhance the risk stratification and make the continuation of the hospital stay short by reducing the demand for additional non-invasive stress tests so as to disclose residual myocardial ischemia.[19] FFR-directed revascularisation was conducive to achieve the best medical treatment and decrease healthcare costs.

A prior meta-analysis by Briasoulis and colleagues failed to show that there was a substantial statistical significance between the FFR and CA groups in MI, MACE, all-cause mortality,[15] and major bleeding because only one study was included about major bleeding in their meta-analysis. There were no significant differences in FFR-directed revascularisation compared to CA-directed revascularisation in the incidence of major bleeding and all-cause mortality. However, the meta-analysis showed a significance difference between the FFR-directed management of NSTEACS patients and the CA-directed management of NSTEACS patients in reducing the incidence of MI.

There are several limitations to consider, when explaining the research outcomes. First, because of being devoid of professional RCTs paying attention to this topic, statistics were only obtained from observational studies, surely leading to inherent bias, equal design bias, selection bias, treatment bias, and publication bias. Second, instead of using an individual ill-patient-level statistic, concluded published event rate was applied for every study, then confounding factors and selection bias could not be wiped out in these studies and some clinical findings are under the control of between-study heterogeneity. Finally, the specific method of CABG or PCI could not be reasoned out. Nevertheless, in spite of the limitations, this data cater to crucial demand for an all-round comparison between the two guided methods, which could improve informed decision-making for the sick patients and physicians to choose an ideal method for revascularisation in sick patients with NSTEACS.

CONCLUSION

FFR-directed management of NSTEACS patients could significantly reduce the incidence of MI, which would improve the quality of life of patients, reduce the re-hospitalisation rate, and lower medical expenses. There was no statistical significance in the incidence of death, or all-cause mortality, MACE, and major bleeding due to limited data from randomised studies. If future large-scale researches will prove these outcomes, then the decrease in MACE related to FFR-directed revascularisation will probably be more obvious.

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