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PII: S1553-8389(17)30047-7
DOI: doi: 10.1016/j.carrev.2017.01.014
Reference: CARREV 993

To appear in: *Cardiovascular Revascularization Medicine*

Received date: 12 January 2017
Accepted date: 20 January 2017

Please cite this article as: Nagaraja Vinayak, Mamas Mamas, Mahmoudi Michael, Rogers Campbell, Curzen Nick, Change in angiogram-derived management strategy of patients with chest pain when some FFR data are available: How consistent is the effect?, *Cardiovascular Revascularization Medicine* (2017), doi: 10.1016/j.carrev.2017.01.014

Change in angiogram-derived management strategy of patients with chest pain when some FFR data are available: how consistent is the effect?

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Conflicts of Interests: None

Key Words: FFR, Coronary Artery Disease

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Abstract

Background: The assessment of patients presenting with angina using invasive angiography alone is imperfect. By contrast, fractional flow reserve (FFR) allows for assessment of lesion-specific ischaemia, which is predictive of clinical outcome. A series of studies has demonstrated that the availability of FFR data at the time of diagnostic angiography leads to significant differences in the management of those patients.

Hypothesis: The objective of this paper is to describe assess the consistency in the difference in management resulting from an FFR-directed versus and angiogram-directed strategy in appropriate observational and randomised trials.

Methods: A methodical search was made using MEDLINE, Current Contents Connect, Google Scholar, EMBASE, Cochrane library, PubMed, Science Direct, and Web of Science.

Results: Eight studies were identified using the eligibility criteria. A total of 2468 patients were recommended to have optimal medical therapy (OMT) alone after initial angiographic assessment but, after FFR results were available, a total of 716 (29.0%) were referred for revascularisation (PCI 626 patients (25.36%); CABG 90 patients (3.64%)). Similarly, 3766 patients were originally committed to PCI after initial angiography: of these 1454 patients (38.61%) were reconsidered to be suitable for OMT alone and 71 individuals (1.8%) were deemed suitable for CABG after FFR data were available. Further, of 366 patients referred for CABG based on angiographic data, the availability of FFR data changed the final decision to OMT alone in 65 patients (17.76%) and PCI in 51 patients (13.9%). Overall, the angiogram-derived management was changed in 22-48% of these study populations when FFR data were available.

Conclusions: Some use of FFR during coronary angiography alters the angiogram-directed management in a remarkably consistent manner. These data suggest that routine use of FFR at the diagnostic angiogram would improve patient care.

Introduction

It is now well established that assessment of patients presenting with cardiac-sounding chest pain based upon angiography alone is flawed.(1, 2) Specifically, the coronary anatomy at angiography does not inevitably reflect the presence and extent of myocardial ischaemia, which is recognised as the best indicator of the cause of symptoms and near term prognosis, and thus represents the clearest target for revascularisation.(1) This is due to a discrepancy between the anatomical assessment of lesion severity and the presence or absence of lesion-level ischaemia.(3) Lesion-level ischaemia is measured by pressure wire assessment using fractional flow reserve (FFR). The ability of FFR measurement to predict clinical outcome has been established in a variety of randomised clinical trials. In the deferral of percutaneous coronary intervention (DEFER) study, the practice of deferring percutaneous coronary intervention (PCI) in lesions that had been identified as requiring PCI based upon angiographic appearances, but were FFR negative, was shown to be safe and associated with a better clinical outcome than stenting them.(4, 5) Furthermore, in patients who had been listed for multi-vessel PCI, the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial demonstrated a reduced incidence of the combined clinical endpoint of death, non-fatal myocardial infarction, and repeat revascularization at 1 year, as well as lower cost, in an FFR-directed strategy compared to an angiogram-directed approach, despite fewer lesions being stented.(6) Fractional Flow Reserve Guided Percutaneous Coronary Intervention Plus Optimal Medical Therapy Versus Optimal Medical Therapy (FAME 2) trial subsequently demonstrated a reduced rate of unplanned revascularisation in patients with FFR positive lesions who were stented compared to a cohort treated with optimal medical therapy alone.(7)

Despite these robust data, the uptake of FFR in routine clinical practice has been lower than expected in patients already being considered for PCI, with rates as low as 6.6% reported in large PCI registries.(8) Furthermore, a series of predominantly observational studies has been

published that demonstrate the ability of FFR to modify the management of patients who are undergoing diagnostic angiography for the investigation of chest pain (ie at an earlier stage in their management pathway.(9-16)

The aim of this paper is to describe the degree to which some use of FFR affects the angiography-derived management strategy for patients in these studies.

Methods

Eligibility criteria

Using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines(17) published studied were recognized that describe the effect of the availability of FFR on an angiogram-derived management of patients being investigated for chest pain.

Search strategy

A methodical search was made using MEDLINE, Current Contents Connect, Google Scholar, EMBASE, Cochrane library, PubMed, Science Direct, and Web of Science to October 2016. We used the following search MeSH terms: acute coronary syndrome; angina; coronary angiography; fractional flow reserve or pressure wire assessment; decision making; outcome assessment. No language restrictions were made. The references of the included publications and relevant review articles were checked for additional relevant studies.

Study selection and data extraction

Three reviewers (VN, MM and NC) independently checked all titles and abstracts for studies potentially meeting the inclusion criteria. The full reports of these studies were retrieved, and we analysed these studies in a qualitative manner in order to describe the number of patients involved, clinical setting, effect of FFR on assessment of lesion level significance and effect of FFR on angiogram-derived management plan.

Quality assessment

The quality of publications was rated using the Quality Assessment Tool for Case Series Studies based on the National Heart, Lung, and Blood Institute (NHLBI).(18)

Results

Description of studies included in analysis

Eight studies have been identified that fit our prespecified criteria. The studies were published between 2007-2016 and report data derived from between 200 – 3093 patients (Figure 1). Seven of the studies were observational and 1 was randomised.(9-16) Seven were derived from invasive angiography and intracoronary FFR measurement and one study is based on CT coronary angiography and FFR_{CT}. In 4 studies the patients were elective only, in 1 study only acute coronary syndrome patients were included and in 3 there was a mixture. The angiographic lesion characteristics representing triggers for FFR measurement varied (range: $\geq$30% up to $\leq$90%) between studies, as did the number of vessels targeted (range: further assessment of at least one intermediate lesion to FFR of all vessels of a diameter that was suitable for PCI).

Quality assessment in included studies

Quality Assessment Tool for Case Series Studies(18) was used to gauge the quality of evidence and all studies were of good quality. Their detailed evaluation has been tabulated in table 2.

Relationship between FFR measurement and change in management plan

The availability of some FFR data in these studies resulted in a change in management in between 22-48% of patients. In all cases this was due to a discrepancy between the anatomical and physiological assessment of lesion-specific significance. In 4 studies, the

authors provide data on the number of lesions whose significance was changed once FFR data were available, and this ranged from 32-48%.

Sant'Anna et al(9) reported data through analysis of lesions (ie lesion-level) whilst all other studies(9-16) reported outcomes based on patient-level data. Overall outcomes based on pooled patient data are described here. A total of 2468 patients were recommended to have optimal medical therapy (OMT) alone after initial angiographic assessment but, after FFR results were available, 626 patients (25.36%) of them were in fact referred for PCI and 90 patients (3.64%) for surgical revascularization (CABG). Similarly, 3766 patients were originally committed to PCI after initial angiography: of these 1454 patients (38.61%) were reconsidered to be suitable for OMT alone and 71 individuals (1.8%) were deemed suitable for CABG after FFR data were available. Further, of 366 patients referred for CABG based on angiographic data, the availability of FFR data changed the final decision to OMT alone in 65 patients (17.76%) and PCI in 51 patients (13.9%). Lastly, in patients in whom further information/functional test (n=254) was recommended after angiography alone, this was deemed unnecessary after FFR data were available, with patients being allocated to OMT alone (47.2%), PCI (39.4%) and CABG (13%). The tables 3, 4 and figure 2 illustrate in detail the effect on angiography-derived management of FFR data.

Only 2 studies reported clinical event data, and the effect of FFR data upon the angiogram-derived outcome.(13, 14) Firstly, in the Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction (FAMOUS-NSTEMI) trial, which was randomised, there was no significant difference in clinical events in either group.(14) Specifically, 8.0% of patients in the FFR-guided group and 8.6% in the angiography-guided group experienced cardiac death, non-fatal myocardial infarction or heart failure hospitalization (P = 0.89). Major adverse cardiac events excluding MI related to revascularization occurred in 5.7% of patients in the FFR-guided group and

2.9% patients in the angiography-guided group (P =0.25). By contrast, the Danish registry reported that FFR-guided PCI was associated with a significantly lower rate of MI (49% relative risk [RR] reduction P value:0.015), MI-driven TLR (59% RR reduction P value:0.045) and 40% RR reduction in the combined endpoint death/MI(P value:0.011) as compared to an angiography-guided strategy.(13) Further, a similar degree of effect for the FFR-guided strategy on the death/MI endpoint was seen in all of the clinical subgroups studied (stratified by age, gender, diabetes, extent of coronary disease, cardiovascular risk factors, chronic renal disease).

Discussion

This meta-analysis reports the consistency with which the availability of some FFR data at the diagnostic angiogram results in a change in the management strategy that is applied to patients with chest pain derived from angiographic data alone. Specifically, in between 22-48% of patients in these study populations there was a change in the recommended angiogram-derived strategy.

The reason for this is a consistent mismatch between the angiographic assessment of lesion severity, and therefore "significance" as a potential target for revascularisation, and the binary allocation that is derived from FFR measurement (ie FFR positive or negative). Recently, several publications(14, 15, 19, 20) have illustrated this important issue. One study(20) showed that a diameter stenosis of more than 50% stenosis was not efficient in identifying a functionally significant lesion (FFR<0.80) with a sensitivity of 61%, specificity of 67% and accuracy of 64%. A detailed analysis from the FAME trial(19) showed that 35% of the 50% to 70% stenosis, 80% of the 71% to 90% stenosis and 96% of the 91% to 99% stenosis category were functionally significant with a FFR of ≤0.80. Curzen et al(15) had comparable results with 53% of >70% stenosis, 33% of 51%-70% stenosis, 33% of 31% and

50%, and 13% of 0%-30% stenosis were functionally significant with a FFR of <0.80. Given this consistent discrepancy between the angiographic appearance of individual lesions and their physiological "significance", it is predictable that the management of patients with chest pain would be optimised by adoption of FFR measurement in a higher proportion of them at the time of their original diagnostic angiogram.

Measurement of FFR in coronary arteries has been unequivocally shown to be predictive of outcome in terms of acute cardiac events and requirement for revascularisation.(3) A series of randomised trials has established that FFR measurement allows for symptomatically and prognostically beneficial outcome by directing PCI revascularisation at both a patient- and lesion-specific level. These trials have, in the process, highlighted the flaws associated with a patient pathway based upon angiographic lesion assessment alone. Despite these data, uptake of FFR remains limited to a small minority of patients undergoing diagnostic angiography in routine clinical practice. For example, in a recent analysis derived from the unselected London PCI registry,(8) only 2767 patients out of 64,232 patients who underwent PCI had pressure wire assessment (6.6%).

Given the demonstrable ability of FFR measurement to influence PCI-based revascularisation in patients who had previously undergone diagnostic angiography, it is logical to consider the potentially wider benefit of applying this concept to patients at the earlier stage in the care pathway when the original diagnostic angiogram is being undertaken. Application of FFR data at the diagnostic stage has the potential to influence all management outcomes, whether based upon OMT or revascularisation, at both patient- and lesion-specific levels. This concept has now been explored in several recent studies that include a variety of designs, patient groups, and indications for FFR. However, despite this heterogeneity, they report a highly consistent effect to modify the angiogram-derived management plan in between 22-48% of the patients included.

The relatively poor uptake of FFR at the stage of diagnostic angiography is explained by many factors. These include perceived concerns about cost and safety, reluctance to increase the procedure time and complexity, poor education or awareness of the potential advantage to patients, reluctance to downgrade candidates for PCI to OMT, the lack of a definitive randomised trial testing the hypothesis in patients at diagnostic angiography.

The health economics of FFR has been assessed in three different healthcare systems namely the United States,(21) United Kingdom(22) and Australia.(23) The analysis from the FAME trial(21) revealed a significant reduction in mean overall cost 2385 USD (P<0.001) in FFR arm compared to the angiographic arm at end of 12 months and this robust result was maintained across subgroups. In addition, among 5000 samples a bootstrap simulation analysis showed FFR guided strategy to be cost saving in 90.74% and attained cost effectiveness at 99.96% (threshold of $50,000/ quality-adjusted life-year gained). A similar analysis conducted in the Australian health system demonstrated that the impact of FFR guided PCI's cost effectiveness was substantial with a total cost savings ranging from 1.8 to 14.5 million AUD over a period of 24 months.(23) However, in the health economic analysis of the FAMOUS-NSTEMI trial from the United Kingdom(22) demonstrated a minor increase in cost of £112 and an increase in quality-adjusted life years by 0.02.

Recently, using complex novel computer modelling it has become possible to derive FFR from CT coronary angiography, termed FFR_{CT}. This has been tested in a series of diagnostic accuracy studies and offers the promise of assessing patients coronary and physiology non-invasively. One of the studies included in this paper, FFR_{CT} RIPCORD, tested the effect that having FFR_{CT} available had on the CT angiogram-derived management plan of 200 cases.(12) The result was that management changed in 36% of cases, which is entirely consistent with the degree of change seen in the exclusively invasive studies included here,

and again was clearly due to the discrepancy between the angiographic and physiological assessment of the significance of an individual lesion.

There are a number of limitations of this study. Firstly, the studies described are heterogeneous in terms of design, patient demographic and lesions included as triggers for FFR measurement. This perhaps makes the consistency of the effect of FFR on management all the more convincing. Secondly, only one of the reported studies was randomised, although, once again, the results obtained from it are entirely consistent with the other data. Third, we cannot report the specific degree in discrepancy between the angiographic and lesion assessment in all these studies, because the data are only available in 4 of them.

The implications of this consistency in the effect of FFR data availability in addition to the angiogram alone on patient management are potentially of clinical significance. In contemporary front line clinical practice only a minority of patients with chest pain who undergo diagnostic angiography are offered FFR assessment at that time. It is likely that a substantial proportion (perhaps between 22-48%?) of such patients have a management plan made that is suboptimal according to the premise that it is patient- and lesion-level ischaemia that represents the dominant target for an outcome benefit relating to revascularisation. Further data about the role of FFR as a routine component of the diagnostic angiogram are now required from appropriately powered randomised trials such as RIPCORD 2 (NCT02892903), but even before such trials have reported there is a strong case that FFR measurement could, and indeed should, be used to tailor therapy more accurately to the benefit of our patients.

Name	Country	Study type	Study period	Inclusion criteria	Exclusion criteria	Year
Sant'Anna et al(9)	Brazil	Prospective	October 2004 to April 2005	Elective PCI	Transmural acute myocardial infarction (AMI) in the last 7 days, chronic total occlusion, or angiographically significant left main disease	2007
Curzen et al The RIPCORD Study(15)	United Kingdom	Prospective	NA	Stable cardiac-sounding CP included the presence in any epicardial vessel of ≥2.25 mm diameter of a ≥30% stenosis	Failure to provide written informed consent, participation in other clinical studies, previous CABG, acute coronary syndrome at presentation, diagnostic angiography or PCI within the previous 12 months, contraindication to adenosine, severe valve disease, serum creatinine >180 μmol/L, and life-threatening comorbidity	2014
Nakamura et al, CVIT-DEFER Registry(11)	Japan	Prospective	December 2012 and September 2013	Angiographically intermediate to moderate coronary stenosis and in whom FFR was clinically indicated	NA	2014
Layland et al, FAMOUS–NSTEMI trial(14)	United Kingdom	Prospective	October 2011 to May 2013	NSTEMI and with at least one risk factor for coronary artery disease (e.g. diabetes mellitus) within 72 h of the index episode of myocardial ischaemia or if there was a history of recurrent ischaemic symptoms within 5 days. ≥1 coronary stenosis ≥30% of the lumen diameter assessed visually	Presence of ischaemic symptoms that were not controlled by medical therapy, haemodynamic instability, MI with persistent ST elevation, intolerance to anti-platelet drugs, ineligible for coronary revascularization, 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), a life expectancy, 1 year and an inability to give informed consent.	2014
Van Belle eta l, FFR-R3F study(16)	France	Prospective	October 2008 to June 2010	NA	NA	2014

Baptista et al, POST-IT Multicenter Registry(10)	Portugal	Prospective	March 2012 to November 2013	NA	Unwillingness to provide written informed consent and life expectancy <1 year because of known noncardiovascular comorbidity	2016
De Backer et al(13)	Denmark	Prospective	1 July 2010 and 30 June 2014	Stable angina pectoris (AP) and at least one 50-89% coronary stenosis were selected	NA	2016
Curzen et al The FFRCT RIPCORD Study(12)	United Kingdom	Prospective	NA	Stable cardiac-sounding CP included the presence in any epicardial vessel of ≥2.25 mm diameter of a ≥30% stenosis	Failure to provide written informed consent, participation in other clinical studies, previous CABG, acute coronary syndrome at presentation, diagnostic angiography or PCI within the previous 12 months, contraindication to adenosine, severe valve disease, serum creatinine >180 μmol/L, and life-threatening comorbidity	2016

Name	No. Patients	% Female	Mean Age, years	Follow up period	Setting	Diabetes mellitus	% Multivessel disease	Unstable angina pectoris	ACS%	FFR Limit	Stenosis Limit	Number of diameter stenosis >70%
Sant'Anna et al(9)	250	38%	61	NA	Elective	23%	70%	7%	0%	0.75	>50%	327
Curzen et al The RIPCORD Study(15)	200	25%	64	NA	Elective	NA	NA	NA	0	0.8	>30%	68
Nakamura et al, CVIT-DEFER Registry(11)	3093	26.2	69.5	NA	Elective & ACS	37.7	34.8	7.2	1.4	0.8	50-90%	NA
Layland et al, FAMOUS–NSTEMI trial(14)	350	24.6	62.3	12 months	ACS	14.8	29	0	100	0.8	>30%	63.1
Van Belle eta l, FFR-R3F study(16)	1075	24.70%	64.7	12 months	Elective & ACS	35.8	47.6	NA	19.5	0.8	35-65%	NA
Baptista et al, POST-IT Multicenter Registry(10)	918	23.7	65.1	12 months	Elective & ACS	35	37.5	4.4	35.4	0.75-0.8	Intermediate	31.9
De Backer et al(13)	1,716	28.8	64.5	23.2 months	Elective	23.8	32.5	0	0	0.8	50-89%	74

Curzen et al The FFRCT RIPCORD Study(12)	200	NA	NA		Elective	NA	NA	NA	0	0.8	>70%	126

Table 1: Clinical characteristics of the publications included in the systematic review

Criteria	Sant'Anna et al(9)	Curzen et al The RIPCORD Study(15)	Nakamura et al, CVIT-DEFER Registry(11)	Layland et al, FAMOUS–NSTEMI trial(14)	Belle eta l, FFR-R3F study(16)	Baptista et al, POST-IT study(10)	Backer et al(13)	Curzen et al The FFRCT RIPCORD Study(12)
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly and fully described, including a case definition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were the cases consecutive?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were the subjects comparable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

5. Was the intervention clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the length of follow-up adequate?	NA	NA	NA	Yes	Yes	Yes	Yes	NA
8. Were the statistical methods well described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the results well described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Quality Rating	Good	Good	Good	Good	Good	Good	Good	Good

Table 2: Quality assessment of the studies

Table 3: Management decisions after angiography and FFR

	Results				Angiographic Intention				FFR Intention				Adverse Events	Additional contrast	Additional screening time
Name	Number of lesions with FFR	Change in management	Lesion Change	Data based on	Medical treatment	Percutaneous Revascularization	Surgical Revascularization	Further information/functional test	Medical treatment	Percutaneous Revascularization	Surgical Revascularization	Further information/functional test			
Sant'Anna et al(9)	452	48%	32%	Lesions	102	350	0	0	158	294	0	0	NA		
Curzen et al The RIPCORD Study(15)	NA	26%	32%	Patients	72	90	23	15	89	80	30	1	0.02 %	70 mL (interquartile range, 140)	342 seconds (interquartile range,526)
Nakamura et al, CVIT-DEFER Registry(11)	3709	39%	NA	Patients	1066	1963	64	0	1496	1520	77	0	NA	NA	NA
Layland et al, FAMOUS–NSTEMI trial(14)	NA	22%	NA	Patients	18	144	14	0	40	125	11	0	NA	NA	NA
Van Belle etal, FFR-R3F study(16)	NA	43%	NA	Patients	587	409	79	0	619	342	114	0	NA	NA	NA
Baptista et al, POST-IT Multicenter	1285	44%	45%	Patients	360	319	38	201	438	404	76	0	NA	NA	NA

Registry(10)															
De Backer et al(13)	NA	31%	48%	Patients	298	754	140	0	596	468	128	0	NA	NA	NA
Curzen et al The FFRCT RIPCORD Study(12)	NA	36%	NA	Patients	67	87	8	38	113	78	9	0	NA	NA	NA

Table 4: Relationship between FFR measurement and change in management plan

	Data based on	Post FFR management	Medical treatment	Percutaneous Revascularization	Surgical Revascularization	Further information /functional test
		Post angiography management				
Sant'Anna et al(9)	Lesions	Medical treatment	58	44	0	0
		Percutaneous Revascularization	100	250	0	0
		Surgical Revascularization	0	0	0	0
		Further information/functional test	0	0	0	0
Curzen et al The RIPCORD Study(15)	Patients	Medical treatment	63	6	3	0
		Percutaneous Revascularization	24	64	2	0
		Surgical Revascularization	1	3	19	0
		Further information/functional test	1	7	6	1
Nakamura et al, CVIT-DEFER Registry(11)	Patients	Medical treatment	694	350	22	0
		Percutaneous Revascularization	788	1157	18	0
		Surgical Revascularization	14	13	37	0
		Further information/functional test	0	0	0	0
Layland et al, FAMOUS–NSTEMI trial(14)	Patients	Medical treatment	13	4	1	0
		Percutaneous Revascularization	25	117	2	0
		Surgical Revascularization	2	4	8	0

		Further information/functional test	0	0	0	0
Van Belle eta l, FFR-R3F study(16)	Patients	Medical treatment	393	153	41	0
		Percutaneous Revascularization	196	180	33	0
		Surgical Revascularization	30	10	39	0
		Further information/functional test	0	0	0	0
Baptista et al, POST-IT Multicenter Registry(10)	Patients	Medical treatment	261	83	16	0
		Percutaneous Revascularization	79	229	11	0
		Surgical Revascularization	7	9	22	0
		Further information/functional test	91	83	27	0
De Backer et al(13)	Patients	Medical treatment	269	23	6	0
		Percutaneous Revascularization	316	433	5	0
		Surgical Revascularization	11	12	117	0
		Further information/functional test	0	0	0	0
Curzen et al The FFRCT RIPCORD Study(12)	Patients	Medical treatment	59	7	1	0
		Percutaneous Revascularization	26	61	0	0
		Surgical Revascularization	0	0	8	0
		Further information/functional test	28	10	0	0

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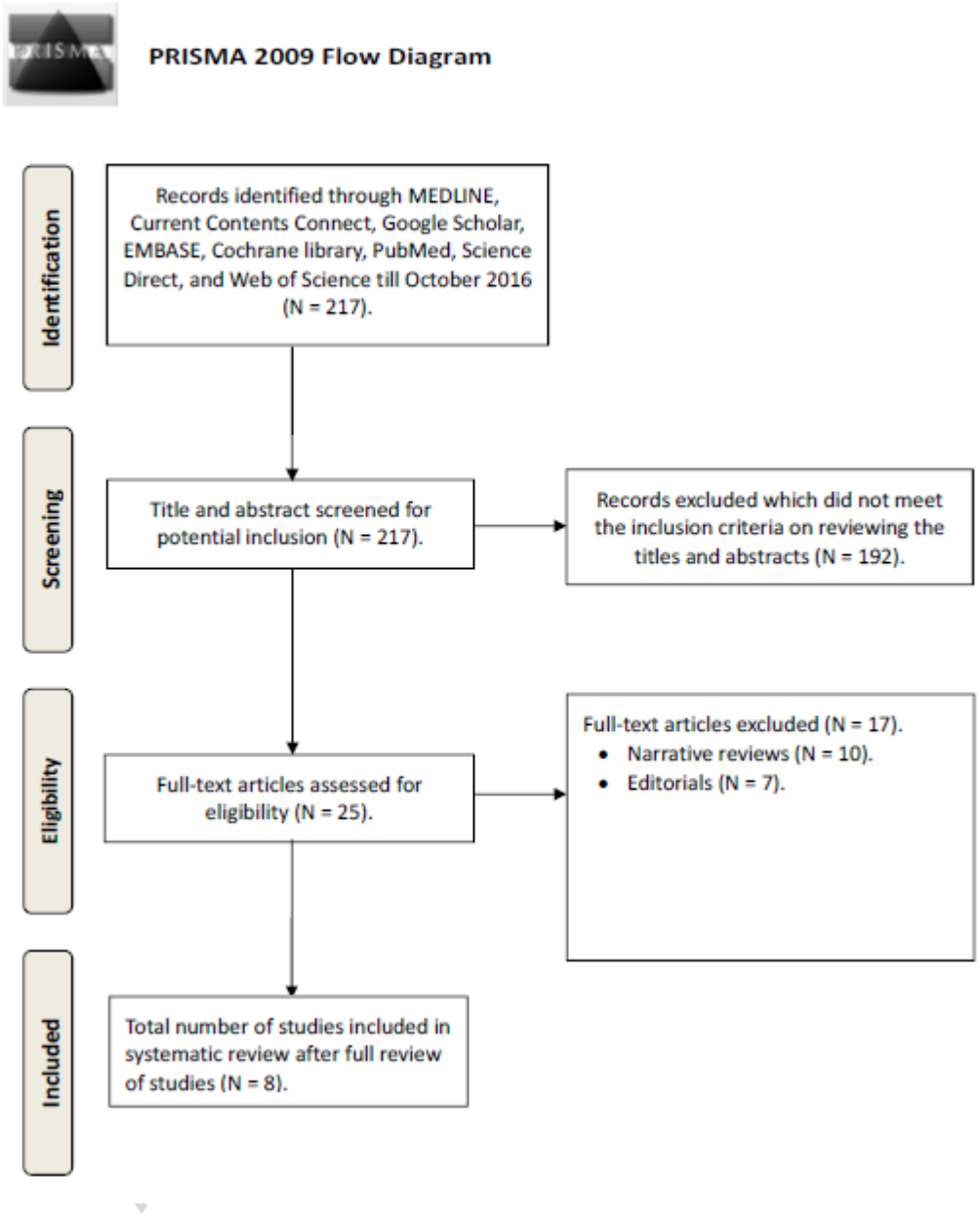

Figure 1 PRISMA Flow Diagram of included publications

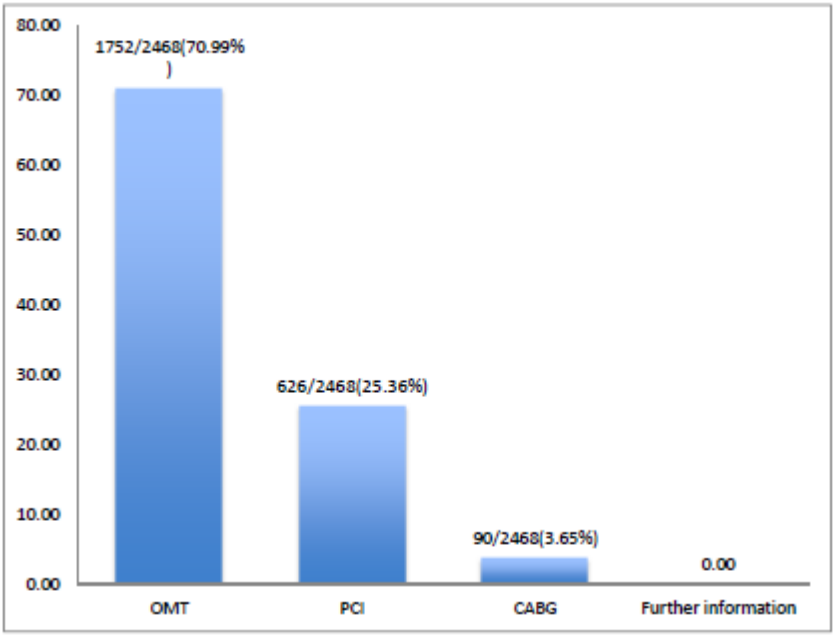

Figure 2A: Reclassification of management strategy after pressure wire assessment subgroup: optimal medical therapy (OMT= optimal medical therapy CABG = coronary artery bypass surgery and PCI=percutaneous coronary intervention)

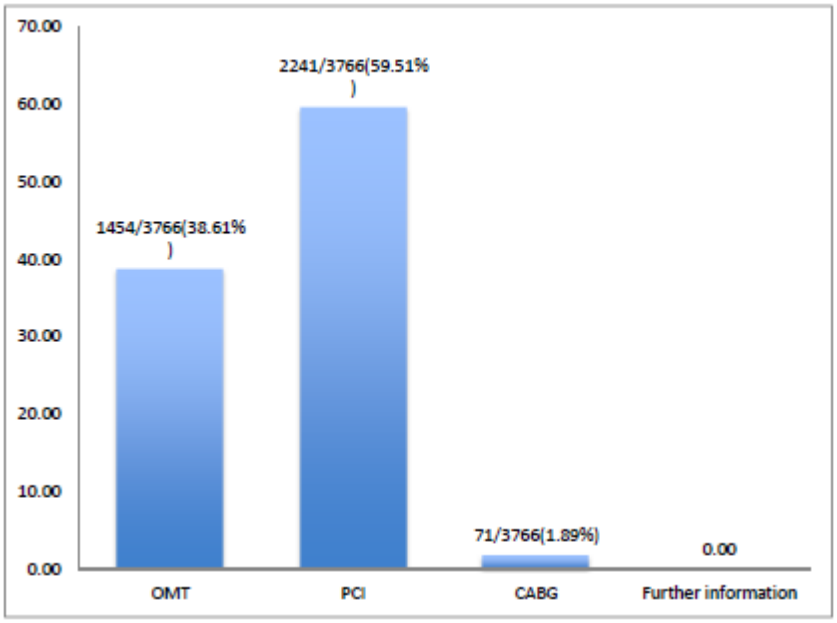

Figure 2B: Reclassification of management strategy after pressure wire assessment subgroup: percutaneous coronary intervention (OMT= optimal medical therapy CABG = coronary artery bypass surgery and PCI=percutaneous coronary intervention)

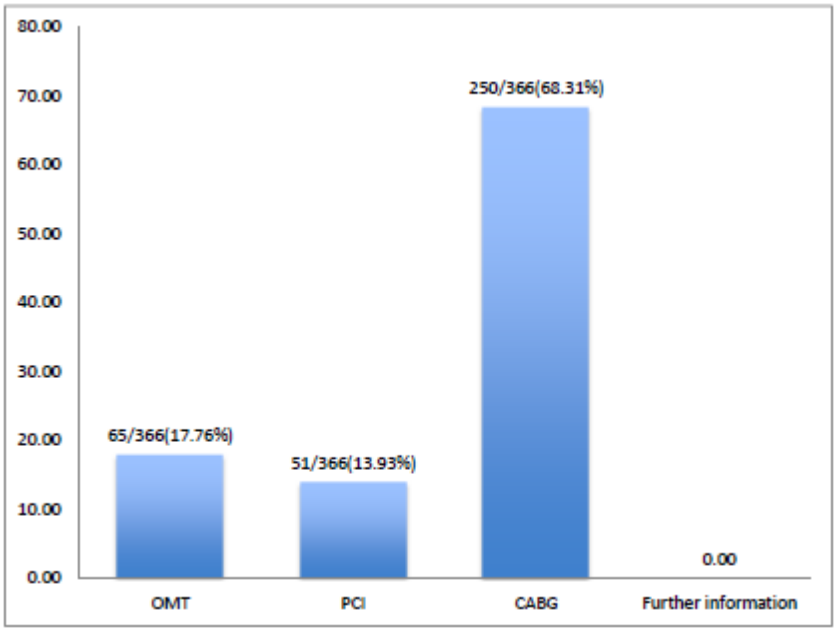

Figure 2C: Reclassification of management strategy after pressure wire assessment subgroup: coronary artery bypass surgery (OMT= optimal medical therapy CABG = coronary artery bypass surgery and PCI=percutaneous coronary intervention)

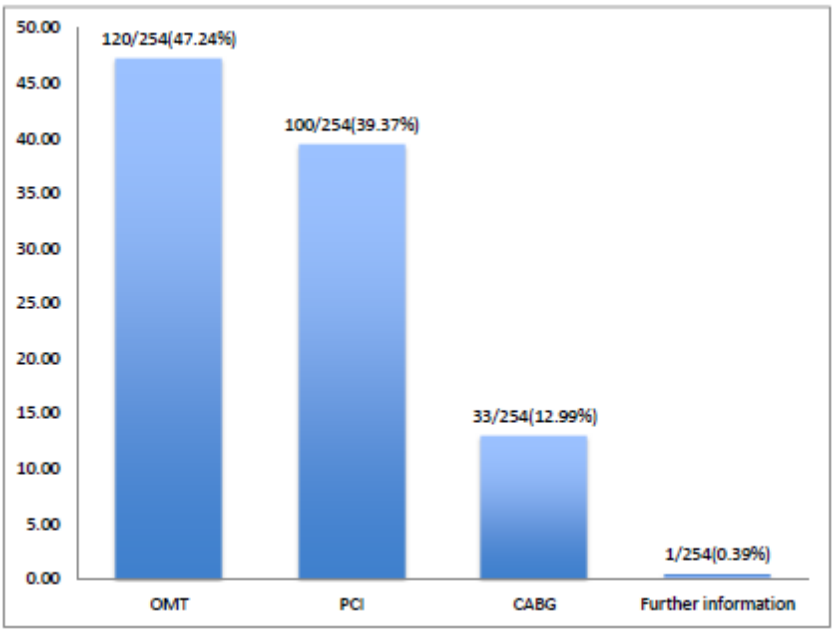

Figure 2D: Reclassification of management strategy after pressure wire assessment subgroup: further information/functional test (OMT= optimal medical therapy CABG = coronary artery bypass surgery and PCI=percutaneous coronary intervention)