Fractional Flow Reserve-Guided Strategy in Acute Coronary Syndrome. A Systematic Review and Meta-Analysis

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Abstract

Background: There are limited data on the prognosis of deferral of lesion treatment in patients with acute coronary syndrome (ACS) based on fractional flow reserve (FFR).

Objectives: To provide a systematic review of the current evidence on the prognosis of deferred lesions in ACS patients compared with deferred lesions in non-ACS patients, on the basis of FFR.

Methods: We searched Medline, EMBASE, and the Cochrane Library for studies published between January 2000 and September 2017 that compared prognosis of deferred revascularization of lesions on the basis of FFR in ACS patients compared with non-ACS patients. We conducted a pooled relative risk meta-analysis of four primary outcomes: mortality, cardiovascular (CV) mortality, myocardial infarction (MI) and target-vessel revascularization (TVR).

Results: We identified 7 studies that included a total of 5,107 patients. A pooled meta-analysis showed no significant difference in mortality (relative risk [RR] = 1.44; 95% CI, 0.9–2.4), CV mortality (RR = 1.29; 95% CI = 0.4–4.3) and TVR (RR = 1.46; 95% CI = 0.9–2.3) after deferral of revascularization based on FFR between ACS and non-ACS patients. Such deferral was associated with significant additional risk of MI (RR = 1.83; 95% CI = 1.4–2.4) in ACS patients.

Conclusion: The prognostic value of FFR in ACS setting is not as good as in stable patients. The results demonstrate an increased risk of MI but not of mortality, CV mortality, and TVR in ACS patients. (Arq Bras Cardiol. 2018; [online].ahead print, PP .0-0)

Keywords: Acute Coronary Syndrome/physiopathology; Percutaneous Coronary Intervention/methods; Coronary Angiography/methods; Fractional Flow Reserve Myocardial/physiology; Microvessels; Vascular Resistance; Reproducibility of Results.

Introduction

Fractional flow reserve is a well-validated, effective technique to determine the functional significance of intermediate coronary lesions; FFR-guided percutaneous coronary intervention (PCI) improves clinical outcomes in patients with stable coronary disease.1-3 Although robust data supports FFR use in stable coronary disease, its use in acute coronary syndrome (ACS) is less well investigated because maximal hyperemia is required to accurately measure FFR. In patients with ACS, microvascular changes may prevent vasodilatation thus affecting the validity of FFR.4-6 These changes appear to be vessel-dependent (culprit vs. non-culprit) and related to the type of infarction – ST-elevation myocardial infarction (STEMI) vs. non-ST-elevation myocardial infarction (NSTEMI).7 FFR values in the culprit vessel are recognized to be higher when measured during acute episodes than when measured after the microcirculation has had some time to recover. Higher FFR values are assumed to be caused by reduced levels of hyperemia in the culprit vessel due to embolization of thrombus and plaque, ischemic microvascular dysfunction and myocardial stunning. Hence, efficacy of the use of FFR in culprit artery disease remains uncertain.8,9

Multivessel coronary disease (MVD), observed in approximately 30-50% of patients presenting with STEMI and in 30-59% with NSTEMI, is associated with a poor prognosis.10,11 Complete revascularization of hemodynamically significant vessels identified in the hemodynamic laboratory early after acute event appears attractive: this approach provides the patient with a well-defined, definitive therapeutic plan. However, several studies suggest that a FFR-guided revascularization strategy in ACS reduces the rate of coronary revascularization without compromising short-term safety.12-15 However, the results of this approach are inconsistent in several studies involving patients with non-ACS.13,14

Therefore, the aims of this study are to provide a systematic review of the current evidence of the deferral of PCI based on FFR in ACS patients and compare it with that supporting this decision in non-ACS patients.

Methods

Data sources and searches

We systematically searched MEDLINE, EMBASE, and the Cochrane Library for relevant articles published between
January 2000 and September 2017. Previous qualitative and systematic reviews, if available, were searched for additional studies. The query terms “Flow Fractional Reserve” OR “Acute Coronary Syndrome” were used in the search. References of the studies identified by the search strategy were reviewed for potentially relevant articles not identified by the above search. No language restrictions were enforced.

Study selection

The title/abstract of citations were first screened by 2 independent reviewers (JM and VA), and complete manuscripts were retrieved if considered potentially relevant. Additional studies were identified by reviewing the bibliographies of included studies and relevant reviews. Disagreements were resolved by consensus. The same reviewers independently appraised identified articles according to the following inclusion criteria: studies that compared clinical outcomes of lesions after PCI deferred based on FFR between ACS patients and non-ACS patients (Figure 1).

Endpoints

The endpoints studied were: mortality, cardiovascular mortality, myocardial infarction (MI), and target vessel revascularization (TVR) during the follow-up period. TVR of the target vessel was defined as subsequent revascularization of the index vessel by either PCI or bypass grafting. In all trials, in the ACS group, distinction between culprit and non-culprit lesions was based on the operator’s discretion, and hence subjective, similar to clinical practice.

Results

Study identification

The search strategy initially retrieved 129 citations. Of these, 96 articles were excluded after review of the title or abstract. After assessment or the studies for the selection criteria, we excluded an additional 26 studies. A total of 7 studies met criteria for the meta-analysis, involving 5,107 (3,540 non-ACS and 1,567 ACS) patients.

Figure 1 – Flowchart of studies included in the meta-analysis.
Four important pathophysiological considerations need to be considered when comparing the FFR results in ACS patients to those of non-ACS patients:

- **Microvascular dysfunction:** The timing of FFR measurement in the ACS patient is an important issue. As described above, immediately after MI, the initial, temporary microvascular injury caused by the inflammatory environment may artificially elevate the initial FFR measurements.Antithrombotic therapy, administered for 3 to 4 days to stabilize the plaque, may reduce microvascular dysfunction, and FFR may then reflect the true hemodynamic situation. This approach of waiting > 5 days to measure FFR in ACS patients was suggested by the European Society of Cardiology guidelines. However, most referral centers that study FFR in ACS perform early invasive evaluation of ACS patients, within 48 h of presentation, a practice that could lead to artificially higher FFR values. 

- **Plaque instability:** At least two-thirds of lesions arising from vessels with < 50% stenosis are responsible for unstable syndromes involving plaque instability, assuming that these vessels previously had normal flow. A non-flow-limiting culprit lesion may be "anatomically significant" but "physiologically nonsignificant", and because FFR is not intended to evaluate plaque characteristics, care must be taken in the use of FFR in vessels with unstable characteristics but normal flow. 

- **Myocardial mass involved:** The mass of viable myocardium being perfused by the artery in question is relevant pathophysiologically to the interpretation of FFR results in ACS patients. The FFR value is inversely proportional to the ejection fraction: hence, a lower ejection fraction, which implies a large area of infarction with less viable myocardium, could produce a higher FFR reading for the same degree of stenosis.

- **Presentation type of ACS:** Because ACS describe a range of myocardial ischemic states with distinct clinical and pathophysiological characteristics, the use of FFR should be differentiated by type of ACS. 

**Characteristics of included studies**

Of the 7 studies included, 1 was a prospective study and 6 had an observational, retrospective in design (Table 1 and Table 2).

**Quantitative synthesis of outcomes**

**Mortality:** We included 3 studies, a total of 2,074 patients, in the pooled analysis. The forest plot (Figure 2) shows the weighted meta-analysis for relative risk (RR) of mortality in ACS patients in comparison with non-ACS patients when revascularization decisions were based on FFR. Pooled analysis showed negligible heterogeneity among the studies (I² = 0%; p = 0.78) and the ACS and non-ACS patients did not differ significantly; their pooled RR was 1.44 (95% CI = 0.89–2.35). Exclusion of any single study did not significantly alter the overall combined result.

**Cardiovascular mortality:** We included 5 studies, a total of 3,144 patients, in the pooled analysis. The forest plot (Figure 2) describes the weighted meta-analysis for mortality risk of basing revascularization decisions on FFR. Pooled analysis showed significant heterogeneity among the studies (I² = 70%; p = 0.01) and the ACS and non-ACS patients did not differ significantly; their pooled RR was 1.29 (95% CI = 0.39–4.25). Exclusion of any single study did not significantly alter the overall combined result.

**Myocardial Infarction:** 7 studies were included, a total of 5,107 patients, in the pooled analysis. Deferring lesions based on FFR was associated with a significant additional risk of MI (RR = 1.83; 95% CI = 1.39–2.40) in ACS patients versus non-ACS patients. Figure 2 describes the weighted meta-analysis of MI. The pooled analysis showed negligible heterogeneity among the studies (I² = 0%; p = 0.96).

**Target-vessel revascularization:** We included 5 studies, a total of 3,475 patients, in the pooled analysis. The forest plot (Figure 2) describes the weighted meta-analysis of TVR in patients when revascularization decisions were based on FFR. Pooled analysis showed negligible heterogeneity among the studies (I² = 39%; p = 0.16). ACS and non-ACS patients did not differ significantly in RR of TVR; their pooled RR was 1.46 (95% CI = 0.93–2.29).

**Study Bias**

Visual inspection of the funnel plots for the outcomes did not reveal any asymmetry among the studies. Further, the Begg rank correlation test was not statistically significant.

**Discussion**

This report provides a systematic review and a meta-analysis comparing the strategy in patients in whom lesion treatment was deferred based on FFR, and no revascularization was undertaken in ACS patients to that in non-ACS patients. FFR-guided revascularization in ACS patients appears to be as safe as in non-ACS patients. In a meta-analysis, evaluated FFR-guided management in NSTE-MI patients, where a modest reduction in incidence of MI was noted, with no significant differences in incidence of major adverse cardiac events (MACE), death or all-cause mortality, and target-vessel revascularization between the FFR-guided approach in comparison with coronary angiography-guided approach.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Follow up</th>
<th>Study design</th>
<th>Total FU</th>
<th>Age (yrs)</th>
<th>Men</th>
<th>Non-ACS</th>
<th>ACS</th>
<th>STEMI</th>
<th>NSTEMI/UA</th>
<th>FFR value used to defer</th>
<th>Median time between Clinical presentation and FFR measurement</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potvin JM et al</td>
<td>2006</td>
<td>11 ± 6 months</td>
<td>Retrospective cohort</td>
<td>201</td>
<td>62 ± 10</td>
<td>131</td>
<td>61</td>
<td>124</td>
<td>11</td>
<td>113</td>
<td>≥ 0.75</td>
<td>24 hours (range 2 to 144)</td>
<td>NR</td>
</tr>
<tr>
<td>Fischer J et al</td>
<td>2006</td>
<td>12 months</td>
<td>Retrospective cohort</td>
<td>111</td>
<td>ACS → 58 ± 14</td>
<td>Non-ACS → 63 ± 10</td>
<td>72</td>
<td>76</td>
<td>35</td>
<td>11</td>
<td>24</td>
<td>≥ 0.75</td>
<td>Recent (within 7 days) ST segment elevation MI treated with lytic Therapy</td>
</tr>
<tr>
<td>Sels et al</td>
<td>2011</td>
<td>2 years</td>
<td>Prospective cohort</td>
<td>1005</td>
<td>ACS → 64.8 ± 10.7</td>
<td>Non-ACS → 64.3 ± 10</td>
<td>744</td>
<td>677</td>
<td>328</td>
<td>0</td>
<td>328</td>
<td>≥ 0.80</td>
<td>NR</td>
</tr>
<tr>
<td>Mehta et al</td>
<td>2015</td>
<td>3.4 ± 1.6 years</td>
<td>Retrospective cohort</td>
<td>674</td>
<td>ACS → 63.8 ± 11.9</td>
<td>Non-ACS → 65.3 ± 10.2</td>
<td>380</td>
<td>340</td>
<td>334</td>
<td>7</td>
<td>327</td>
<td>&gt; 0.80</td>
<td>NR</td>
</tr>
<tr>
<td>Hakeem A et al</td>
<td>2016</td>
<td>3,4 ± 1,6 anos</td>
<td>Retrospective cohort</td>
<td>576</td>
<td>ACS → 66.6 ± 8</td>
<td>Non-ACS → 64.7 ± 8.7</td>
<td>554</td>
<td>370</td>
<td>206</td>
<td>0</td>
<td>206</td>
<td>&gt; 0.75</td>
<td>NR</td>
</tr>
<tr>
<td>Van Belle et al</td>
<td>2017</td>
<td>1 year</td>
<td>Retrospective cohort</td>
<td>958</td>
<td>ACS → 66 ± 11.2</td>
<td>Non-ACS → 66.4 ± 10</td>
<td>693</td>
<td>721</td>
<td>237</td>
<td>-</td>
<td>-</td>
<td>&gt; 0.75 e &gt; 0.80</td>
<td>NR</td>
</tr>
<tr>
<td>Lee JM et al</td>
<td>2017</td>
<td>722 days</td>
<td>Retrospective cohort</td>
<td>1596</td>
<td>ACS → 62.0 ± 11.1</td>
<td>Non-ACS → 62.4 ± 9.4</td>
<td>1112</td>
<td>1295</td>
<td>301</td>
<td>0</td>
<td>301</td>
<td>&gt; 0.80</td>
<td>NR</td>
</tr>
</tbody>
</table>

FU: Follow-up; yrs: years; ACS: acute coronary syndrome; STEMI: ST segment elevation myocardial infarction; NSTEMI: non-STEMI myocardial infarction; FFR: fractional flow reserve; PCI: Percutaneous coronary intervention; MI: Myocardial Infarction; TVR: target vessel revascularization; CABG: Coronary artery bypass grafting; NR: not reported.
MVD patients; the rate of major adverse cardiac events (defined as cardiac mortality or hospitalization for MI or heart failure) was 7.5% in patients with deferred PCI based on FFR and 0% in those deferred PCI based on angiography.13

The aim of this analysis was not to evaluate FFR-guided decisions per-lesion level, but rather to focus on the relevance of FFR-guided decision per-patient level, considering that patients with ACS frequently have more than 1 lesion suitable for revascularization and the identification of the culprit lesion is not always straightforward. Undoubtedly, patients with MVD have worse outcomes than patients who present with single vessel disease. The natural history of patients who are revascularized in an acute setting is known to differ from those who are revascularized in a stable setting.13 For example, the probability of malignant dysrhythmias is significantly more common in acute patients and is an important cause of mortality.13

This systematic review and meta-analysis summarizes all published studies that assessed and compared clinical outcomes of ACS and non-ACS patients with deferred lesion treatment based on fractional flow reserve.14

When MI injury (defined as any MI attributable to a deferred revascularization based on the index FFR) was specifically evaluated, deferring treatment of lesions based on FFR did not differ significantly in the RR of MI injury between ACS and non-ACS patients [RR 1.84 (95% CI = 0.82–4.11); (I2 = 0%; p = 0.98)] (Figure 3).

If on the one hand, Briasoulis et al.15 showed that a FFR-guided strategy in ACS seems to be associated with a better prognosis compared to an angiography strategy, the primary finding of our study was that deferring the treatment of lesions was associated with an increased risk of MI in ACS patients compared to non-ACS patients, represented by the RRs of the target-vessel revascularization or MI lesion.15 In addition, mortality and CV mortality did not differ between ACS and non-ACS patients.

Our results are consistent with the recently published study by Van Belle et al.,38,39 who compared the impact differing the management of intermediate lesions, based on FFR, on the prognosis of ACS vs. non-ACS patients from two important registries, R3F and POST-it. They concluded that revascularization decisions based on FFR for differing treatment of lesions were safe in ACS patients.38-40

Some authors have questioned whether we should be less permissive and adopt a different cut-off value for FFR in unstable vessels. Hakeem et al.,44 recently determined that the best FFR cut-off value for predicting MI or TVR was > 0.80 in patients with stable coronary artery disease, supporting current practice. However, in NSTE-ACS patients, the best cutoff value was > 0.84. However, some limitations suggested by some authors deserve consideration in interpreting their results. For example, it is unclear why mortality, the most important outcome, was not included in the composite endpoint in this study. In addition, medical therapy was not optimal for the patients, 14% of patients did not receive statin,

Table 2 – Clinical outcomes of ACS and non-ACS patients with deferred lesion treatment based on fractional flow reserve

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients [FFR &gt; cutoff] *</th>
<th>Mortality</th>
<th>CV Mortality</th>
<th>Myocardial infarction</th>
<th>Target lesion revascularization</th>
<th>Target vessel revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pothov JM et al</td>
<td>2006</td>
<td>ACS → 124 Non-ACS → 61</td>
<td>NR</td>
<td>ACS → 0</td>
<td>ACS → 2</td>
<td>ACS → 11</td>
<td>ACS → 7</td>
</tr>
<tr>
<td>Fischer J. et al</td>
<td>2006</td>
<td>ACS → 35 Non-ACS → 76</td>
<td>ACS → 3</td>
<td>ACS → 2</td>
<td>ACS → 1</td>
<td>ACS → 6</td>
<td>ACS → 7</td>
</tr>
<tr>
<td>Sels et al.</td>
<td>2011</td>
<td>NR</td>
<td>ACS → 12</td>
<td>Non-ACS → 20</td>
<td>Non-ACS → 36</td>
<td>ACS → 45</td>
<td>ACS → 72</td>
</tr>
<tr>
<td>Mehta et al.</td>
<td>2015</td>
<td>ACS → 334 Non-ACS → 340</td>
<td>ACS → 23</td>
<td>Non-ACS → 8</td>
<td>ACS → 47</td>
<td>ACS → 78</td>
<td>ACS → 66</td>
</tr>
<tr>
<td>Hakeem A et al</td>
<td>2016</td>
<td>ACS → 206 Non-ACS → 370</td>
<td>ACS → 9</td>
<td>Non-ACS → 30</td>
<td>ACS → 16</td>
<td>ACS → 36</td>
<td>ACS → 14</td>
</tr>
<tr>
<td>Van Belle et al</td>
<td>2017</td>
<td>ACS → 237 Non-ACS → 721</td>
<td>ACS → 10</td>
<td>Non-ACS → 17</td>
<td>ACS → 3</td>
<td>ACS → 15</td>
<td>ACS → 14</td>
</tr>
<tr>
<td>Lee JM</td>
<td>2017</td>
<td>ACS → 301 Non-ACS 1295</td>
<td>NR</td>
<td>ACS → 3</td>
<td>Non-ACS → 5</td>
<td>ACS → 8</td>
<td>ACS → 10</td>
</tr>
</tbody>
</table>

ACS: acute coronary syndrome; CV: cardiovascular; NR: not reported; *Cut-off values varied from 0.75 to 0.80 among the studies; ** Sels et al.46 evaluated whether there is a difference in benefit of fractional flow reserve (FFR) guidance for percutaneous coronary intervention (PCI) in multivessel coronary disease in patients with acute coronary syndrome (ACS) vs. non-ACS without discriminating those patients with FFR > 0.80; *** Target-vessel revascularization was not specified.
and approximately two-thirds did not receive dual antiplatelet therapy. Moreover, several technical issues might explain the higher FFR cut-off values reported in these studies.\textsuperscript{34,41-43}

Despite most of the studies included did not report clinical outcomes by type of lesions (culprit or non-culprit) lesions, available evidence suggests, as previously mentioned, that in patients with ACS, microvascular dysfunction may be less marked, and the ability to achieve maximal hyperemia is sufficient to maintain the diagnostic use of FFR, both in culprit and non-culprit vessels.\textsuperscript{44}
Besides that, due to the great heterogeneity of inclusion criteria, follow-up period and the vessel assessed by FFR, results and conclusion of the current study should be the interpreted with caution.

Limitations
The conclusions drawn from this meta-analysis are subject to the limitations and differences of the original studies included in the analysis. First, our meta-analysis included both randomized clinical trials and (mostly) observational studies. The conclusions of this study may be somewhat limited due to biases inherent in the observational studies, including design, selection, and treatment bias. Another possible limitation is the potential publication bias because the results only included short-term mortality.

Conclusion
The prognostic value of FFR in ACS setting is not as good as in stable patients. More homogeneous studies with larger populations of patients are necessary to reach definitive and robust conclusions. Careful definition and interpretation of the clinical results is important when analysis of FFR is not performed in patient-level but in vessel-level only.

Acknowledgements
We thank the CIDMA - Center for Research and Development in Mathematics and Applications of the University of Aveiro for the statistical analysis, and the Portuguese Foundation for Science and Technology (FCT - Fundação para a Ciência e a Tecnologia) (project UID/MAT/04106/2013).

Author contributions
Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Martins JL; Statistical analysis: Martins JL, Afreixo V; Critical revision of the manuscript for intellectual content: Martins JL, Afreixo V, Santos J, Gonçalves L.

Potential Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Sources of Funding
There were no external funding sources for this study.

Study Association
This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate
This article does not contain any studies with human participants or animals performed by any of the authors.

References


Estratégia guiada por reserva de fluxo fracionada na SCA

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