Biochemical risk assessment and invasive strategies for acute coronary syndromes without ST-segment elevation
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Chapter 3

Percutaneous Coronary Intervention for Non ST-Elevation Acute Coronary Syndromes: Which, When and How?

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ABSTRACT

The presentation of patients with suspected Non ST-Elevation Acute Coronary Syndrome (NSTE-ACS) is quite diverse. Therefore, the diagnostic build-up and choice of treatment may vary accordingly. Major issues regarding the evaluation are the likelihood of the diagnosis and the risk of adverse events. Both of these factors should guide the choice of diagnostic test. Patients with an increased risk of ischemic events and patients with recurrent ischemia are most likely to benefit from revascularization. In addition, when Percutaneous Coronary Intervention (PCI) is considered, evidence suggests that sufficient time should be allowed for pharmacological stabilization, reducing the possibility of periprocedural inflicted Myocardial Infarction (MI). However, postponement of intervention may lead to an increase of new spontaneous events and high risk patients should apply for revascularization soon after pharmacological stabilization. The extent of revascularization performed by PCI predominantly depends on patient characteristics and anatomy, but should be limited to flow obstructive lesions. In conclusion, patients presenting with NSTE-ACS consist of a very diverse population; diagnostic workup, treatment and timing of a possible intervention should be tailored to the individual.
INTRODUCTION

Patients with chest pain represent a large and increasing proportion of all acute medical presentations worldwide. Of all those presented for evaluation, only a minority has an acute coronary syndrome (ACS). Distinguishing which patients have an ACS remains a diagnostic challenge. The principal pathophysiological mechanism of an ACS is myocardial underperfusion which results from atherosclerotic plaque rupture or erosion with different degrees of superimposed thrombus. The ECG provides the initial classification. Patients are divided into those with persistent ST segment elevation (STEMI) and patients without persistent ST-segment elevation or non ST-elevation acute coronary syndrome (NSTE-ACS). This article discusses the diagnostic challenges when NSTE-ACS is suspected. In addition, it will address the role of risk stratification in relation to the choice of treatment strategy. When an invasive approach is preferred, an important issue is the timing of the intervention. The available evidence on this topic will be discussed in detail. The review will conclude with the evidence regarding the type and extent of revascularization in patients with multivessel disease.

Diagnostics and Risk Assessment

In patients presenting with a suspected NSTE-ACS, 2 major issues have to be addressed. This first challenge is to confirm the diagnosis. Guidelines recommend the use of elementary tools such as: the patients’ symptoms, the risk profile for coronary artery disease, electrocardiography (ECG) and biomarkers to estimate the likelihood of disease. In addition echocardiography in the acute phase can be used to clarify the diagnosis. However, sometimes the diagnosis remains uncertain. In these cases, the clinical probability of an ACS should be assessed. Although both ACC/AHA and ESC guidelines do not provide guidance on this topic, the next diagnostic test of choice should depend on the likelihood of disease. In Figure 1 an algorithm is proposed in which the preferred performance of the diagnostic test is related to the estimated probability of a NSTE-ACS. In case of a low clinical probability patients are to be discharged safely, therefore a diagnostic test should be used with a high sensitivity and high negative predictive value. Ischemia testing such as exercise testing with or
without imaging modality is frequently used in the subacute setting. However, such
tests are most useful in patients with an intermediate probability of an ACS. In our
opinion, poor performing tests, such as treadmill or bicycle exercise testing, should
be restricted to prognostic purposes only. Despite being not recommended by the
current ESC guidelines, computed tomography angiography (CTA) is at present the
most accurate non-invasive test to rule out coronary artery disease (CAD).\textsuperscript{1,5} New
sophisticated scan protocols, using prospective ECG gated triggering, substantially
reduce radiation exposure (effective dose value approximately 3 mSv), without
reducing the image quality.\textsuperscript{6} Extra cardiac findings such as pulmonary tumors,
-embolism and aortic dissection can also be detected.\textsuperscript{7} In selected patients with acute
chest pain, the diagnostic accuracy of CTA is excellent.\textsuperscript{8} In addition, this approach is
more cost effective and less diagnostic time consuming.\textsuperscript{9}

In case of a high probability of ACS, patients should be admitted to the hospital for
clinical follow up and treatment. In these patients false positive results are more
likely to occur. Accordingly, the diagnosis ACS should only be waived based on tests
with both high sensitivity and specificity: invasive coronary angiography currently
being the golden standard. In this population, coronary angiography is able to exclude
coronary artery disease reliably. This should be strived for, because even in the
presence of ECG changes and troponin rise, about a fifth of the patients suspected
of high risk NSTE-ACS show no significant lesions on a coronary angiography.\textsuperscript{10,11}
These patients generally have a low risk, and should be evaluated for alternative
pathologies.

Due to the absence of validated scoring systems to estimate the probability of NSTE-
ACS in patients with chest pain, there is limited information on the distribution of
the eventual diagnoses over the various levels of suspicion of ACS. A small trial by
Goldstein et al. evaluated the use of CTA in about 200 patients with chest pain and
a low probability of ACS.\textsuperscript{9} The mean TIMI risk score was 1.2. The amount of patients
diagnosed NSTE-ACS was about 10%, the remainder had non-cardiac chest pain. The
amount of patients who underwent PCI was 4% and who required CABG 2%.\textsuperscript{9} In the
OPTIMA trial, about 250 patients with suspected intermediate to high-risk NSTE-
ACS underwent acute coronary angiography.\textsuperscript{11} The mean TIMI risk score was: 3.8. Of
these 78% was diagnosed NSTE-ACS, the remainder had non-cardiac chest pain. Of
all patients 55% was treated with PCI and 10% underwent CABG.
Algorithms showing the clinical application of diagnostic tests according to the probability of the Non-ST-Elevation Acute Coronary Syndrome.


The second issue to be addressed in patients with suspected NSTE-ACS involves risk assessment. Patients with NSTE-ACS represent a prognostic heterogeneous group. Therefore, risk stratification plays a central role in evaluation and management. For
this purpose multiple scoring models have been developed with the GRACE and TIMI risk score being the most widely used. Both models show a strong relationship between indicators of the likelihood of an NSTE-ACS and prognosis\textsuperscript{12,13} The GRACE risk tool was developed on the basis of data from the large multinational cohort study: Global Registry of Acute Coronary Events (GRACE) and validated in subsequent GRACE and GUSTO IIb cohorts.\textsuperscript{12,14} Recently, the GRACE score was prospectively revalidated in a large contemporary cohort.\textsuperscript{15} The TIMI score was developed using data from the TIMI 11B trial\textsuperscript{13} and prospectively validated in several cohorts, including that of the TACTICS-TIMI 18 trial.\textsuperscript{16} The GRACE score estimates the risk of death up to 6 months and the TIMI risk score addresses the 14 day risk of death, recurrent myocardial infarction (MI) or urgent revascularization. This risk estimation, together with individual patient characteristics, should further guide the treatment strategy.

**Indications for Urgent Revascularization**

A subset of patients with NSTE-ACS are considered to have such an increased mortality risk that immediate revascularization is recommended.\textsuperscript{1,2} These include cardiogenic shock, severe left ventricular dysfunction, suspected left main stem disease, recurrent or refractory ischemia in rest despite intensive pharmacological treatment, mechanical complications such as acute mitral regurgitation, and sustained VT’s. This recommendation is based on a single study which suggested a better outcome with revascularization in patients presenting with cardiogenic shock.\textsuperscript{17} However, most patients can be medically stabilized. These patients should be evaluated for an invasive approach.

**Routine Invasive versus Selective Invasive Therapy**

In the last two decades, multiple trials have evaluated different clinical strategies regarding coronary angiography and subsequent revascularization of clinically stabilized NSTE-ACS patients. Two general approaches have emerged: The first being the ‘early invasive’ or ‘routine invasive’ strategy, involving a routine early coronary angiography followed by revascularization when appropriate. The other is the ‘conservative’ or ‘selective invasive’ approach, with initial pharmacological management and coronary angiography followed by revascularization for recurrent
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ischemia only. This new ischemia may either be spontaneous or provoked by non-invasive stress testing.\(^1,2\) Currently, both AHA/ACC and ESC guidelines support a routine invasive management in intermediate to high risk NSTE-ACS patients.\(^1,2\)

Four large randomized controlled trials have dominated the debate on the routine performance of invasive diagnostics in NSTE-ACS. The results, unfortunately, were quite diverse. (Table 1) In 1999 the FRISC 2 trial, showed a significant reduction in the combined endpoint of death and MI with the routine invasive approach.\(^18\) The observed difference was mainly driven by an excess in MI in the selective invasive group. The TACTICS-TIMI 18 trial, published in 2001 showed similar results: a decrease in MI, but no significant mortality benefit.\(^16\) In 2003 the RITA 3 trial failed to show any benefit for death or MI.\(^19\) Ultimately, in 2005 the ICTUS trial was published.\(^20\) This study, with optimal medical treatment in both arms, showed an increased MI risk in the routine invasive arm with no difference in mortality.

Interpretation of the study results is difficult due to important differences in methodology. Foremost, when the studies are compared, there appears to be a marked variation in intensity of revascularization between study arms. (Table 1) The conservative arm of the ICTUS trial showed a revascularization rate which is similar to the routine invasive arm in RITA 3.\(^19,20\) Also, the definition of MI differed between trials. The low biomarker threshold used in the ICTUS trial may partly explain the higher amount of MI in patients requiring PCI.\(^20\)

The improved use of anticoagulants, dual antiplatelet therapy, statins and ACE-inhibitors may also be part of the assumed demise of the routine invasive treatment benefit. This is most clear for the use of statins. In the FRISC 2 and TACTICS-TIMI 18 trials, approximately half the patients received a statin at discharge.\(^16,18\) In RITA 3 this had already increased to 70%, whereby the ICTUS trial provided high dose statin treatment in 92% of the patients.\(^19,20\) Although less outspoken, the use ACE inhibitors showed similar patterns. Based on the ICTUS trial, the current AHA/ACC guideline acknowledges the option of a selective invasive strategy with aggressive medical treatment.\(^2\)
### TABLE 1.
Methodological differences between trials evaluating routine versus selective invasive approach in Non ST-Elevation Acute Coronary Syndromes.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Timeframe patient inclusion</th>
<th>Timing of catheterization in the routine invasive approach</th>
<th>Routine invasive</th>
<th>Selective invasive</th>
<th>Primary trial outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% Revascularization</td>
<td>% PCI</td>
<td>% PCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% Revascularization</td>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RI</td>
</tr>
<tr>
<td>FRISC 2</td>
<td>1996-1998 (6m FUP)</td>
<td>&lt; 7 days</td>
<td>77%</td>
<td>42%</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>94/1207* (7.8%)</td>
</tr>
<tr>
<td>TACTICS TIMI</td>
<td>1997-1999 (6m FUP)</td>
<td>4-48h</td>
<td>64%</td>
<td>42%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53/1114** (4.8%)</td>
</tr>
<tr>
<td>RITA 3</td>
<td>1997-2001 (1y FUP)</td>
<td>&lt;72h</td>
<td>57%</td>
<td>36%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34/895 (4%)</td>
</tr>
<tr>
<td>ICTUS</td>
<td>2001-2003 (1y FUP)</td>
<td>24-48h</td>
<td>79%</td>
<td>61%</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90/604*** (15%)</td>
</tr>
</tbody>
</table>

*p=0.03, **P=0.002, ***P=0.005

FUP: follow up, PCI: percutaneous coronary intervention, RI: routine invasive, SI: Selective invasive
It may not be surprising that long-term (5 year) follow up of the aforementioned trials show discordant results.\textsuperscript{21,22} Remarkably, the initial negative RITA 3 trial suggested a marked 5 year benefit in the routine invasive group regarding death and MI. (OR 0.78 (0.61–0.99), p=0.04).\textsuperscript{23} Indeed, a recent meta-analysis based on individual 5 year follow up patient data from FRISC 2, RITA 3 and ICTUS showed a reduction in MI using the routine invasive strategy.\textsuperscript{24}

The relation between treatment effect and patient risk has been evaluated in subanalyses of several trials. Regardless of the risk score used, there appeared to be a consistent treatment benefit for the invasive approach in high risk patients as compared to low risk patients. Both, FRISC 2, TACTICS TIMI 18 trials as well as the 5 year follow up of RITA 3 showed the greatest benefit of the routine invasive approach in high risk patients.\textsuperscript{16,18,23} This resulted in a wide acceptance of the routine invasive approach is in this subpopulation. The clinical application of the aforementioned TIMI and GRACE-risk scores has been evaluated extensively. Remarkably, recent data from the GRACE registry suggests the presence of an inverse relationship between patient risk and the rate of PCI.\textsuperscript{25} In daily practice, angiographic findings and referral practice may greater influence the decision to proceed to PCI than the patients’ risk status.

In conclusion, the different outcomes in the large trials evaluating the invasive approach in NSTE-ACS mainly reflect both the change in study protocols and pharmacological treatment. For the clinical practice it seems reasonable to consider a liberal selective invasive approach equivalent to a temperate routine invasive approach. The patients with the highest risks for adverse outcomes are thought to derive the greatest benefit from invasive evaluation and revascularization. However, as clinical judgment on risk estimation appears to be challenging, the use of systematic and accurate risk stratification methods seems important.

**Timing of PCI**

The last few years several studies have evaluated the influence of timing of intervention in patients with NSTE-ACS. Once again, comparison of data and interpretation of the results are difficult, mainly due to methodological differences between the studies. (Table 2) Current AHA/ACC and ESC guidelines do not give specific recommendations on this topic.\textsuperscript{1,2}
### TABLE 2.
Methodological differences between trials evaluating timing of invasive approach in Non ST-Elevation Acute Coronary Syndromes.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Timeframe patient inclusion</th>
<th>Early strategy</th>
<th>Time to Catheterization (median)</th>
<th>% PCI</th>
<th>Time to PCI (median)</th>
<th>Delayed strategy</th>
<th>Time to Catheterization (median)</th>
<th>% PCI</th>
<th>Time to PCI (median)</th>
<th>MI Early</th>
<th>mortality delayed</th>
<th>Early</th>
<th>mortality delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR COOL²⁶</td>
<td>2000-2002</td>
<td>2.4h</td>
<td>64% NA</td>
<td>86h</td>
<td>70% NA</td>
<td>21 / 203</td>
<td>21 / 207</td>
<td>3 / 207</td>
<td>0 / 203</td>
<td>(5.9%)</td>
<td>(10.1%)</td>
<td>(1.4%)</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>TIMACS²⁷</td>
<td>2003-2008</td>
<td>14h</td>
<td>60% 16h</td>
<td>50h</td>
<td>55% 52h</td>
<td>57 / 1593</td>
<td>59 / 1438</td>
<td>46 / 1593</td>
<td>47 / 1438</td>
<td>(3.6%)</td>
<td>(4.1%)</td>
<td>(2.9%)</td>
<td>(3.3%)</td>
</tr>
<tr>
<td>OPTIMA¹¹</td>
<td>2004-2007</td>
<td>2h</td>
<td>100% 2.5h</td>
<td>1.8h</td>
<td>99% 27h</td>
<td>44 / 73* (60.3%)</td>
<td>26 / 69 (37.7%)</td>
<td>0 / 73</td>
<td>0 / 69</td>
<td>(60.3%)</td>
<td>(37.7%)</td>
<td>(0%)</td>
<td>(0%)</td>
</tr>
<tr>
<td>ABOARD²⁸</td>
<td>2006-2008</td>
<td>1.1h</td>
<td>80% NA</td>
<td>20.5h</td>
<td>70% NA</td>
<td>16 / 175 (9.1%)</td>
<td>8 / 177 (4.5%)</td>
<td>5 / 175</td>
<td>2 / 177</td>
<td>(9.1%)</td>
<td>(4.5%)</td>
<td>(2.9%)</td>
<td>(1.1%)</td>
</tr>
</tbody>
</table>

*p=0.005  
NA: not available, MI: Myocardial Infarction, PCI: percutaneous coronary intervention
The first study published evaluating the timing of the routine invasive approach is the ISAR-COOL trial. This trial randomized patients with suspected NSTE-ACS to an early (within 24 hours after anginal complaints) or a 3-5 day deferred invasive diagnostic strategy. Although, there was no difference between groups regarding the individual endpoints, the combined endpoint of death and MI occurred significantly less in the early arm when compared to the deferred strategy. Recently, both TIMACS and ABOARD trials provided important information on the feasibility of a very early invasive diagnostic routine. The TIMACS is clearly the largest study performed with approximately 1500 patients in both arms. This study was negative in its endpoints. However, sub-analysis of a high-risk population defined as a GRACE risk score of > 140, suggested a benefit in the early arm. The ABOARD-trial evaluated a primary PCI approach for NSTE-ACS as compared to elective catheterization on the next day. The trial failed to show any benefit for this approach. In addition, there appeared to be a trend towards more MI in the early group.

The influence of timing of PCI remains difficult to determine because the aforementioned trials randomized to timing of coronary angiography and only a part of the patients was treated with PCI. (Table 2) It is likely that the influence of timing of coronary angiography is less pronounced in patients who are treated conservatively or who eventually undergo CABG. It is clear that a fast invasive diagnostic approach has diagnostic benefits and facilitates the logistics of further treatment planning. However, the question remains; should an early angiography always be followed by prompt intervention? The proper answer can only be obtained from a randomized study where patients are randomized between immediate and delayed PCI, as was done in the OPTIMA trial. Although the trial was terminated early due to slow patient recruitment, it suggested the presence of an early hazard. After acute coronary angiography in 251 patients admitted with NSTE-ACS, this trial randomized 142 acute patients eligible for PCI to an immediate (0.5 h) or a deferred (24h) PCI. Moreover, the OPTIMA used only one infarct definition and included all myocardial infarctions in its endpoint, including evolving MI at randomization. This was done because, with very early PCI, periprocedural MI is hard to distinguish from a spontaneous evolving MI that started before PCI. The OPTIMA showed that MI was significantly more common in patients receiving immediate PCI (Table 2).
This difference was most likely due to an excess of periprocedural infarctions in the immediately treated group. This seems to contradict with a recently published post-hoc analysis of the ACUITY trial which suggested a better outcome with urgent revascularization.\textsuperscript{29} Although this study included a large patient sample, the design of the ACUITY trial was not suited to detect the influence of timing of PCI. These observational studies are extremely liable to indication bias and should therefore be interpreted with the utmost caution.

Are there any clues regarding the optimal timing of intervention which can be distilled from the data provided by the 4 trials on this topic? When it is suggested that the influence of timing of invasive therapy is the most pronounced just after an acute event, it is likely that the timing of initiation of therapy in the early invasive group will be the most important variable. In this case, a time-event relationship can be estimated using the relative risk for MI at 30 days for each trial and plotted against the time of admittance to diagnostic catheterization. The latter being at least remotely related to timing of intervention. Figure 2 shows this interpretation which suggests a “U” shaped curve time-event relationship.

With the use of potent antiplatelet and anticoagulation therapy, the early hazard is not as pronounced as in the past.\textsuperscript{30} In the acute setting, PCI is still most likely to counteract plaque passification by intracoronary manipulation leading to a higher rate of periprocedural MI. It seems reasonable to want to treat patients with PCI after pharmacokinetic onset of the initiated medication in order to reduce periprocedural inflicted MI. Therefore, sufficient time is needed to allow for pharmacological stabilization, but postponement of intervention may lead to an increase of new spontaneous events. One may expect that patients at high risk for recurrent events benefit most from revascularization soon after pharmacological stabilization.
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**FIGURE 2**
The relation between timing of the early intervention and the relative risk for myocardial infarction against a delayed strategy at 30 day follow up.

Revascularization Methods

Although numerous clinical trials have compared PCI and Coronary Artery Bypass Grafting (CABG), few trials have compared PCI and CABG in a selected NSTE-ACS patient population. The AWESOME trial randomized NSTE-ACS patients to PCI using bare metal stents (BMS) or CABG. Short and long-term mortality rates were similar, but PCI was associated with an increase in recurrent ischemia and repeat revascularization. The current guidelines recommend CABG for patients with disease of the left main coronary artery, multivessel disease and impaired left ventricular function. Contemporary trials show nevertheless that PCI provides an alternative in patients with less complex coronary artery disease. Although the use of modern stents and scoring systems aid to the feasibility of PCI in high risk patient groups, it remains associated with a higher rate of repeat procedures.

Patients who present with an ACS often show multiple coronary lesions, of which at least one is responsible for the symptoms. These so called culprit lesions can be identified either by angiographic characteristics or by coronary territory. The latter...
requires the determination of the localization of ischemia. In patients with STEMI, multivessel PCI has been associated with an increased rate of ischemic events as compared to PCI of the culprit lesion alone.\(^3^4\) On the other hand, in stable patients no differences in events were observed.\(^3^5\) Although there is a lack of prospective data in patients with NSTE-ACS, a large registry of NSTE-ACS patients treated with PCI showed multivessel revascularization to be equivalent as compared to PCI of the culprit lesion alone regarding death or MI. In this registry, multivessel PCI was associated with a lower rate of repeat revascularization.\(^3^6\) In case of multivessel approach, fractional flow reserve (FFR) guidance should be considered while selective intervention limited to flow obstructive lesions results in a decrease in adverse events.\(^3^7\)

**Future Directions**

In the past 20 years the arise of invasive coronary diagnostics, interventions and pharmacotherapeutics has revolutionized modern cardiology. Strategies based on different pathophysiological assumptions such as plaque sealing\(^3^8\) and primary PCI\(^1^1,2^8\) have been considered. Undeniably, coronary revascularization has played a dynamic role. Future research should focus on better identification of those patients with a high risk of recurrent unstable disease. Plaque composition and morphology using CTA or optical coherence tomography (OCT) are being evaluated as promising new techniques.\(^3^9-4^1\) There is increasing evidence that the use of CTA in patients with suspected NSTE-ACS can provide important information on the pathophysiology of the acute event by recognizing the vulnerable plaque.\(^4^0\) (Figure 3) When an early invasive strategy is preferred, OCT is able to identify underlying plaque morphology and detect thrombi of different stages of organisation.\(^4^1\) How this new insight will influence clinical decision making and whether this will alter the choice of therapy, will be the debate of the forthcoming years.
FIGURE 3
The use of Computed Tomography Angiography in the initial evaluation of a Non ST-Elevation Acute Coronary Syndrome.

This CTA was performed in a 48 year old male presenting with chest pain. There was an intermediate probability of an ACS; Multiplanar reconstruction of the LAD showed a moderate severe mixed stenosis in the proximal LAD with evidence of superimposed thrombus. (White arrow)

ACS: acute coronary syndrome, CTA: computed tomography angiography, LAD: Left anterior descending coronary artery
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