

Routine Primary PCI; Whether and When Necessary for the Management of NSTEMI—An Evidence Based Evaluation

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Abstract

Non ST elevated myocardial infarction (NSTEMI) accounts for a significant portion of the hospitalizations due to acute coronary syndromes worldwide and is posing a huge challenge towards the health care cost globally. This signifies the need for proper triage and management stratification for the best utilization of the health care resources. Primary Percutaneous Coronary Intervention (PCI) with early revascularization is a new emerging invasive technique and application of this technique is increasing tediously among the clinicians. However, the current body of evidences is divided between the efficacy, need and critical timing of PCI compared to conservative management in the treatment protocol for NSTEMI. A review of trials done comparing the early use of PCI versus conservative management indicates inconsistent finding with strong evidence towards early use of PCI in moderate to high-risk NSTEMI patients.

Keywords

Non ST-Elevation Myocardial Infarction (NSTEMI), Percutaneous Coronary Intervention (PCI)

1. Introduction

The clinical phenomenon that occurs due to acute coronary blockage and resultant ischemia in the myocardium is called Acute coronary syndrome (ACS), which is differentiated primarily based on severity into unstable an-

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gina (UA), non ST elevated myocardial infarction (NSTEMI) and ST elevated myocardial infarction (STEMI) [1] [2]. These are pathophysiologically related to each other and commonly caused by instability and rupture of atherosclerotic vulnerable plaques [3] [4]. Only about one fourth of the ACS cases are due to STEMI and the rest majority being either UA or NSTEMI [5]. Some recent studies have found that about 54% of the ACS patients admitted to the hospital have NSTEMI [5]. It has also been found that most of the NSTEMI patients tend to be older with multivessel disease, poor LV function and have higher mortality rate (31%) compared to STEMI patients (21%) [5]. These facts highlight the need of evidence-based approach for the preventive and risk stratified management of the type specific coronary diseases. In this write-up, we will focus mainly on the evidence-based management of NSTEMI with particular emphasis on coronary angiography (with a view to revascularization).

2. NSTEMI

NSTEMI can be defined as a development of heart muscle necrosis following an acute interruption of blood supply due to subtotal occlusion of coronary vessels (e.g. atheromatous plug rupture, dissection, vasculitis, etc.) without any elevation of ST-segment in electrocardiogram (ECG), and can be demonstrated by an elevation of cardiac enzymes (CK-MB, troponin I & T) in the blood [6] [7].

NSTEMI mostly presents with typical anginal pain (constricting, tightening or heavy in character, usually located in the center of the chest, but may radiate to neck, jaw, shoulder, back, and arms) at rest or on minimal exertion but may also present with breathing difficulty, sweating, palpitation or even without any significant symptoms [6]. As there is subtotal coronary artery occlusion, NSTEMI is understandably less severe than STEMI (complete coronary occlusion) [6].

Long standing exposure to the risk factors (like hyperlipidemia, hypertension, smoking, hyperglycemia, abdominal obesity etc.) results in the formation of atherosclerotic plugs [8]. When a vulnerable atherosclerotic plug ruptures, it results in thrombus formation, which causes subtotal occlusion of major coronary arteries or total occlusion of minor coronary arteries causing necrosis of partial thickness of the myocardium. This is the most common mechanism for NSTEMI (shown in **Figure 1**). In about 35% to 75% cases of UA or NSTEMI, there is evidence of a coronary thrombus occluding the infarcted artery, which occurs in more than 90% of the cases of STEMI [9].

Management of NSTEMI

Diagnosis of NSTEMI is mostly made by clinical history, ECG changes and assessment of cardiac enzymes. Treatment of NSTEMI involves urgent in-hospital care by some general and specific means. Medical treatment focused on stabilization of plaque and prevention of progression and prevention of subsequent future events as well as treating the symptoms. On the other hand, revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) aims to re-establish effective coronary blood flow, leading to improvement of myocardial ischemia and its manifestations [10].

I. Medical management

Early supportive measures include: 1) bed rest with continuous monitoring by ECG; 2) inhaled oxygen therapy—if oxygen saturation (%) is low; 3) analgesia (usually opioid analgesics); 4) beta blockers & nitrates; 5) calcium channel blocker (diltiazem, verapamil) for patient having pain in spite of having full dose of nitrate & beta blockers or who have a contraindication to beta blockers; 6) angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs)—to treat hypertension or if there is LV dysfunction; and 7) statins (irrespective of cholesterol level).

Specific medical measures encompass: 1) antiplatelet therapy and 2) antithrombin therapy [11].

• Antiplatelet therapy

1) Aspirin—reduces mortality, 300 mg single loading dose is given unless contraindicated (major bleeding risk or hypersensitivity), clopidogrel should be considered if the aspirin is contraindicated;

2) Clopidogrel—after assessing the adverse cardiovascular risk 300 mg single loading dose is given to all patients along with aspirin and continues for a month. In low risk patients, clopidogrel should be discontinued 5 days before CABG, whereas it can continue before CABG in intermediate to high-risk patients;

3) Glycoprotein IIb/IIIa inhibitors (tirofiban, abciximab, or eptifibatide)—mostly given to the patient with

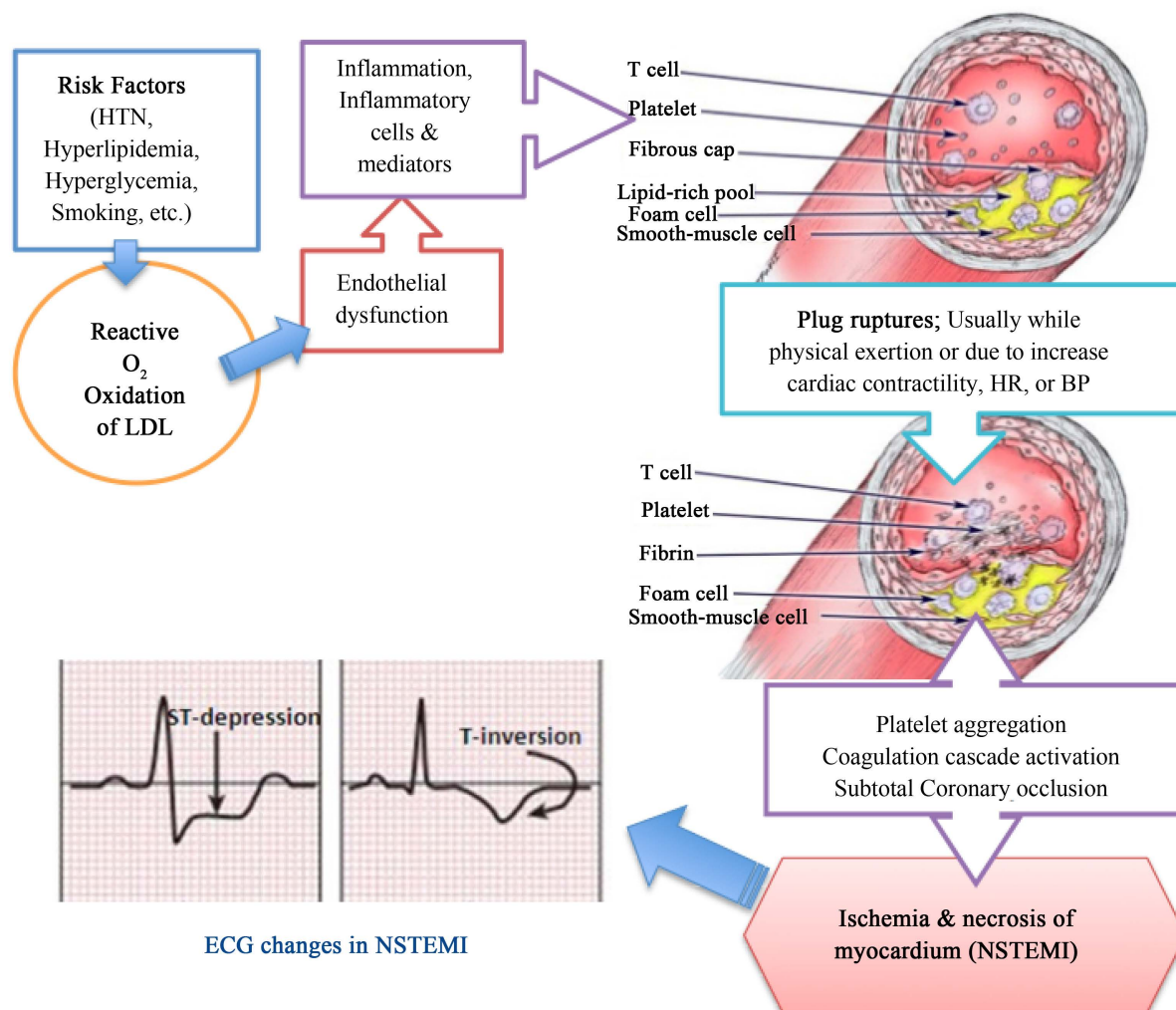


Figure 1. Pathophysiology of NSTEMI.

intermediate to high cardiovascular risk; eptifibatide or tirofiban can be considered for the patient who will undergo angiography within 96 hours of hospital admission and abciximab considered in adjunct to PCI.

- **Antithrombin therapy**

It considered based on patients weight, age, renal function and history of bleeding complications. If there is plan for coronary angiography within 24 hours of admission and there is no significant renal impairment (creatinine above 265 micromoles/liter); unfractionated heparin (dose adjusted based on clotting function) should be consider, otherwise Fondaparinux given as an alternative. Systemic unfractionated heparin (50 - 100 units/kg) can also be given in the cardiac catheter laboratory to patients receiving Fondaparinux who are undergoing PCI. As an alternative to combination of heparin plus GP inhibitors; bivalirudin can be consider for the patients with intermediate or higher risk of adverse cardiovascular events not received a GPI or Fondaparinux yet and scheduled for angiography (with PCI if needed) within 24 hours of admission.

II. Coronary angiography and revascularization

It is an emerging invasive treatment strategy with a view to early revascularize. In this review we will look at the evidences for and against the routine use of early PCI as compared to conservative medical management.

3. Evidences for Routine PCI in NSTEMI

Coronary Angiography is an X-ray imaging of the coronary vessels and is a gold standard for the diagnostic evaluation of the coronary vessels in terms location and severity of atherosclerotic plaques, anatomy of coronary

arteries and providing guideline for the need of therapeutic interventions (medical management, PCI with stent placement or CABG) [12]. In spite of all the benefits, there is a significant risk (1 in 100 to 1 in 1000) of various complications ranging from minor bleeding to life threatening complications like heart attack, stroke, renal failure and death [13]. As such there is critical balance between the two to guide the treatment strategies. With the evidence based medicine approach, the use of coronary angiogram is limited to the cases where the benefit outweighs the risks [4]. Based on this principle, two pathways of treatment emerged for the NSTEMI patients- Early-invasive strategy versus early conservative strategy. In early invasive strategy, all patients without any contraindication undergo coronary angiography followed by revascularization (if needed) within 4 to 24 hours of hospital admission [4]. On contrary, in the early conservative strategy medical therapy is initiated for all patients and coronary angiogram is reserved for those with risk factors like advanced age, history of MI, previous revascularization, heart failure related complications and so on [4].

However, with the advancement of science, modification of clinical techniques, use of drug eluting stents and novel drugs there has been a continuous modification in the guidelines and protocols related to the use of PCI in NSTEMI. Starting from early nineties there has been various large-scale clinical trials worldwide to detect the critical point between early invasive and early conservative strategies as shown in evidence **Table 1**.

4. Discussion

Based on the above-mentioned evidences it is seen that the data is not consistent throughout. Some of the trials like FRISC II, TACTICS-TIMI18, VINO, RITA-3, ISAR-COOL found that in moderate to high risk groups the benefit of early intervention overweighs the early conservative therapy in terms of better overall prognosis, reduced risk of subsequent hospitalization and need of multiple anti-angina medication [4] [14]-[17]. In contrary, trials like TIMI-III B, ICTUS trial, ABOARD showed no significant difference was seen between the two groups. Of the studies which compared immediate versus delayed PCI, most of them found no difference in the timing of PCI with one (ABOARD) finding slightly higher complications with immediate PCI [18]. ISAR-COOL study, which looked at anti-thrombotic pretreatment of PCI, found that early intervention had lesser complication. However, all the trials varied by their patient population, age group, cardiac risk factors, ECG findings, inclusion and exclusion criteria, use of PCI techniques, choice of medical therapies and so on. Hence, the current trials cannot be generalized to the other populations. As such there is a need for more properly designed and generalizable trials to better characterize the treatment protocols.

According to NICE guideline, risk assessment should be done following initial management using GRACE or TIMI Score [11]. As per AHA guideline, the high risk indicators for NSTEMI include: 1) Patients with recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy; 2) Recurrent angina/ischemia with CHF symptoms, an S3 gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation; 3) High-risk findings on noninvasive stress testing; 4) Depressed LV systolic function (e.g., EF < 0.40 on noninvasive study); 5) Hemodynamic instability or angina at rest accompanied by hypotension; 6) Sustained ventricular tachycardia; 7) PCI within 6 months and 8) Prior CABG.

The high to moderate risk NSTEMI patients should be considered for early invasive therapy using PCI or CABG [11]. Intravenous GP IIB/IIIa should be given to all patients undergoing PCI [22]. Early conservative medical therapy should be considered in low risk patients followed by angiography and revascularization for those who are resistant to medical therapy [22]. The indication for PCI includes multivessel coronary disease with suitable coronary anatomy, normal LV Function and without diabetes; one to two vessel coronary disease without significant proximal LAD blockage and with a large area of viable myocardium and high-risk criteria on noninvasive testing [22]. Thus, current evidences favor the use of conservative management in low risk patients and early invasive management for moderate to high-risk NSTEMI patients.

Though in this paper we tried to evaluate all the trials and meta-analyses related to the early PCI for NSTEMI, however there might be other related trials, which were beyond the scope of this paper.

5. Conclusion

The evidence obtained from different trials does not provide a strong generalizable background for the use of early PCI in all NSTEMI cases. Further clinical trials are needed to better justify the use and timeline of PCI in

Table 1. Evidence table for coronary angiography & revascularization (PCI) in NSTEMI [4].

Trial (year)	Coronary events	Population	Treatment	Endpoints	Result	Conclusion
TIMI-IIIb trial (1994) [4]	Unstable Angina (UA)	1473 men and women; Age 21 - 79; have ECG changes of undocumented CAD	Early invasive (PCI) vs. early conservative therapy. PCI done within the first 6 weeks especially in the first 48 hours.	Composite of death, MI or abnormalities on an exercise stress test.	No significant difference in composite endpoint. Significant difference in length of initial hospitalization ($p = 0.01$), incidence or re-hospitalization within 6 weeks ($p < 0.001$) and number of days of re-hospitalization ($p < 0.001$)	Either therapy is appropriate for patient management
FRISC II trial (1999) [14]	NSTEMI	2457 patients from 58 Scandinavian countries.	Early invasive versus early conservative treatment with placebo-controlled long-arm LMWH (deltaparin). Coronary angiography done within 7 days of randomization	Composite endpoint of death or MI.	After 6 months, the incidence of MI or death was significantly lower in early-invasive group ($p = 0.03$). Decrease in angina symptoms and hospital readmission. Highest benefit for the high-risk patients with ST depression in ECG and troponin T levels was at least $0.03 \mu\text{g/L}$. At 5 years follow up the composite endpoints were lower in early invasive group ($p = 0.009$)	Short-term follow up shows early invasive therapy better than early conservative. The 5 years follow up showed sustained benefit of early invasive therapy in moderate to high-risk patients.
TACTICS-TIMI I 18 trial (2001) [4]	NSTEMI	2220 patients aged 18 or more were randomly selected based on ST changes in ECG with raised cardiac biomarker.	Early-invasive treatment strategy (routine coronary angiography and if needed revascularization within 4 to 48 hours of hospital admission) versus a more conservative strategy (medical management and coronary angiography only in patients with spontaneous or inducible Ischemia). All patients received aspirin, heparin & tirofiban.	Composite of death, nonfatal MI, and re-hospitalization for ACS at 6 months	Primary end point is significantly lower in early invasive group ($p = 0.025$). Intervention superior if Troponin T positive ($p < 0.001$) and TIMI score > 3 .	The benefits of the early-invasive strategy was greatest only in medium- and high-risk patients, with elevated cardiac troponin T levels and ECG demonstrating ST-segment change or a TIMI risk score of at least 3. In other cases there was not any significant difference between the groups.

Continued

The VINO Study (2002) [15]	NSTEMI	137 patients were included from 10 centers based on inclusion (ECG change of ST depression) and exclusion criteria.	First day Angiography/angioplasty group versus early conservative group (medical treatment followed by angiography if recurrent MI)	Composite end point of death or recurrent non-fatal MI at 6 months	Six month mortality ($p < 0.03$) or non-fatal reinfarction ($p < 0.02$) was significantly lower in the first day coronary angiography group	First day coronary angiography followed by angioplasty reduces mortality and reinfarction in NSTEMI patients
RITA-3 (2002) [16]	UA or NSTEMI	Multicenter trial of 1810 patients of mean age 62 and 38% women	Early intervention versus conservative strategy. The antithrombin agent in both groups was enoxaparin.	Co-primary endpoints of combined rate of death, non-fatal myocardial infarction, or refractory angina at 4 month. The other endpoint was a combined rate of death or non-fatal MI at year 1	At 4 months, 9.6% of patients in early intervention group versus 14.5% of patients in conservative group died or had MI or had refractory angina. Most of the difference was due to reduction in refractory angina. The rate was similar for both groups at 1 year.	Early intervention is better than conservative approach in NSTEMI patients mainly due to halved refractory angina cases and no increase in rate of death or MI
ISAR-COOL trial (2003) [17]	UA with NSTEMI or elevated cardiac troponin T	410 patients admitted to 2 tertiary care center with symptoms of unstable angina with NSTEMI or elevated cardiac troponin T	Anti thrombotic pretreatment for 3 to 5 days preceding coronary angiography versus early intervention following 6 hours of pretreatment. Antithrombotic included Iv unfractionated heparin, aspirin, clopidogrel and IV tirofiban	Composite 30-day incidence of non-fatal MI or death from any cause	11.6% of Group receiving prolong anti thrombotic pretreatment had primary endpoint compared to 5.9% of group receiving early intervention.	Early intervention with intense anti thrombotic pretreatment has a better outcome compared to the group receiving prolong pretreatment with anti thrombotic
ICTUS trial (2007) [18]	NSTEMI and elevated cardiac troponin T	1200 patients from 42 aged 18 to 80 years with inclusion criteria of symptomatic patient with raised cardiac biomarker and either ischemic change in EKG or documented history of CAD and other exclusion criteria's	Early invasive strategy, including early routine PCI and revascularization when appropriate, versus selective invasive strategy, where PCI was done if the patient had refractory angina or recurrent ischemia	Frequency of death, MI or re-hospitalization after 1 year. Follow up was done at 4 year	At the end of 1 year no difference between the groups with respect to primary endpoint. Similar results were seen at the end of 4 year.	Early invasive strategy not better than selective invasive strategy.

Continued

TIMACS trial (2009) [19]	UA & NSTEMI	Multi-center trial with enrollment of 3031 patients selected based on eligibility criteria (two out of three) of age >60 years, ST segment changes in EKG and raised cardiac biomarker	Early intervention (PCI ≤ 24 hours after randomization) or delayed intervention (PCI ≥ 36 hours after randomization)	The primary outcome was a composite of death, MI or stroke at 6 months. Secondary outcome was death, myocardial infarction, or refractory ischemia at 6 months.	The reduction in the primary outcome was not significantly different between the two groups (p = 0.15). There was a relative reduction of 28% of secondary outcome in early intervention group compared to delayed intervention (p = 0.003) especially in high-risk patients.	Early intervention was better to delayed intervention in reducing the rate of secondary outcome of death, MI or refractory ischemia especially in high-risk patients.
OPTIMA trial (2009) [20]	NSTEMI	Multi-center trial conducted in 3 high-volume centers with PCI facilities. 142 patients >21 years of age with no contraindication to PCI and fulfilling one of the 4 criteria's including raised troponin T, ST depression, CAD and risk factor for CAD	Immediate PCI versus delayed PCI (24 to 48 hours)	The primary endpoint was a composite of death, non-fatal MI or unplanned revascularization, at 30 days. Following discharge patients were followed up at 30 days and 6 months.	At 30 days, the incidence of primary endpoint was 60% in group with immediate PCI compared to 39% in group receiving delayed PCI (p = 0.004). The incidence of MI was significantly higher in the group with immediate PCI (p = 0.005). The observed difference at the end of 30 days was preserved at 6-months' follow-up.	PCI for high-risk patients with NSTEMI should be delayed for at least 24 h after hospital admission
ABOARD trial (2009) [21]	NSTEMI	352 patients with NSTEMI admitted at 13 high-volume centers in France.	Immediate invasive vs. invasive scheduled on the next working day, which means a time window of 8 - 60 hours post enrollment. Abciximab started in both cases before the start of PCI	The primary endpoint was peak troponin level during hospitalization. Secondary endpoint was the composite of death, MI or urgent revascularization at 1 month follow-up.	Both primary and secondary endpoints did not differ much between the two strategies	For patients with NSTEMI there is no difference in occurrence of MI when treated with immediate invasive vs. invasive therapy scheduled on the next day.

NSTEMI. The trials so far provided a basis for the use of PCI only in high to moderate risk NSTEMI patients.

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