"The value of knowledge is qualified and quantified when knowledge is put into action."

Materials & Methods
4: MATERIALS AND METHODS

The clinical studies were carried out at The Heart Care Clinic and SAL Hospital & Medical Institute, Ahmedabad, India. The study protocols were approved by the Institutional Review Board. All the coronary interventional procedures of studies were performed by cardiologists Dr. Keyur Parikh with his team (Care Cardiovascular Consultants). All the participating patients gave written informed consent prior to enrollment. The Case Report Forms were filled for all the patients and baseline demographic details, biochemical and hematological investigations, vital signs and physical examination, patient and family history, cardiovascular risk factors, angiographic data, procedural details, study outcomes, etc. were recorded. The studies were carried out according to Good Clinical Practice as per ICH-GCP and Indian GCP/ICMR Guidelines.

4.1 EVALUATION OF EFFICACY AND SAFETY OF PITAVASTATIN WITH ATORVASTATIN IN HYPERLIPIDEMIC PATIENTS

4.1.1 Study Population:
Males and non-pregnant, non lactating female patients' diagnosed of primary hypercholesterolemia or combined dyslipidemia and who have baseline fasting TG concentration <400 mg/dL and an LDL-C concentration >160 mg/dL after the 4-weeks of dietary lead in period were enrolled into the study. Patients who have agreed for each clinic visit in fasting for 52 weeks were randomized into the study. Exclusion criteria were homozygous familial hypercholesterolemia or familial hypoalphalipoproteinemia, conditions which may cause secondary dyslipidemia, or impaired pancreatic function/injury, liver injury, impaired renal function, and obstruction of the urinary tract or difficulty in voiding due to mechanical as well as inflammatory conditions. Serum creatinine phosphokinase (CK) >5× upper limit of the normal reference range, uncontrolled hypothyroidism, severe acute illness or severe trauma in the last 3 months, significant CVD, history of heart failure, gross cardiac enlargement; significant heart block or cardiac arrhythmias. History of uncontrolled complex ventricular arrhythmias, uncontrolled atrial fibrillation/flutter or uncontrolled supraventricular tachycardias with a
ventricular response rate of >100 beats per min at rest, left ventricular (LV) ejection fraction <25%, history of symptomatic cerebrovascular disease, recent use of supplements known to alter lipid metabolism, hypersensitivity reactions to other HMG-CoA reductase inhibitors, resistant to lipid-lowering drugs. Excessive obesity and signs of mental dysfunction were not randomized into the study.

4.1.2 Study Design:

It was a prospective, randomized, parallel group, open label, single centre study. Following a wash-out dietary lead-in period, 50 patients were randomized to either Group I (pitavastatin, n=25, test drug) or Group II (atorvastatin, n=25, standard drug). Daily calorie intake was tolerated between 1,400 and 1,800 depending on the subject’s health and cholesterol intake was <300 mg/day (diet plan designed by a dietician). A dietary baseline phase was followed by the treatment phase. At the baseline dietary phase, lipid profiles were obtained to determine eligibility. The baseline demographics, hemodynamic, medical and previous cardiac history were assessed and recorded. A baseline physical examination, electrocardiogram, and laboratory assessment was done. Patients with raised pathology parameters from ULN (other than lipoproteins) after dietary compliance during baseline were not randomized into the study.

4.1.3 Study medication & dosage:

Group I:
Test Drug: Pitavastatin - 2 mg/day orally after 30 min of dinner or evening meal for 52 weeks.

Group II:
Standard Drug: Atorvastatin - 10 mg/day orally after 30 min of dinner or evening meal for 52 weeks.

4.1.4 Study Procedure:

Patients meeting the eligibility criteria and dietary compliance were screened for routine pathology tests. Baseline hematology parameters (red blood cell count, white blood cell count, hemoglobin, hematocrit, and platelet count), biochemistry parameters (S. creatinine, urea, uric acid, SGOT and SGPT), biomarkers (CK, CK-MB, Troponin I,
hsCRP, urine myoglobin, TSH and HbA1c) and lipid profile (TC, LDL-C, HDL-C, TG and Apo B) measurements were done before randomization. All the patients were followed clinically on week 12, 24, 36, 48 and 52. Changes in the lipoproteins levels from baseline were measured on week 12, 24, 36, 48 and 52. Hematology, biochemistry and bio markers parameters were measured on week 24 and week 52. All parameters were evaluated following a 12-hour overnight fast.

❖ Concomitant Medications

1. Recommended Concomitant Therapy

   Antihypertensive therapy, hypoglycaemic agents for patients with type 2 diabetes (except glitazones), estrogen modulators (e.g. raloxifene) for osteoporosis prevention were allowed during the course of treatment.

2. Contraindicated Concomitant Therapy

   Medication that interfere with interpretation of the clinical endpoints, agents that lowers or modify plasma lipid levels which included fibric acid derivatives, niacin (nicotinic acid) and other statins, oral contraceptives or any systemic steroid hormones, anticoagulants, cyclosporine, nefezodone, systemic antifungal agents, HIV protease inhibitors, danzol, grapefruit preparations were prohibited.

4.1.5 Clinical endpoints:

Efficacy parameters:

   Primary endpoint of the study was percentage change in LDL-C from baseline at week 24 and 52. Secondary endpoints were percentage change in TC, HDL-C, TG, Apo B, hs-CRP and LDL-C target attainment from baseline on week 12, 24, 36, 48 and 52 (European Atherosclerosis Society [EAS], and National Cholesterol Education Program [NCEP]), safety and tolerability.

Safety parameters

   Clinical abnormal laboratory investigations and ECG examination were evaluated on week 24 and week 52. Adverse events were assessed and recorded; its causal relationship was assessed by the Physician. Urine myoglobin levels were measured on week 12, 24, 36, 48 and 52 during the treatment.
4.2 EVALUATION OF SAFETY AND EFFICACY OF BIVALIRUDIN (ANTITHROMBIN AGENT) WITH HEPARIN AS AN ADJUNCT THERAPY IN MODERATE TO HIGH RISK ISCHEMIC HEART DISEASE PATIENTS PRESENTING WITH ACS AND UNDERGOING PCI

4.2.1 Study Population:
The patients with de Novo lesions of naive coronary vessels meeting the eligibility criteria were enrolled in the study. Patients presenting with chest pain >10 min within 48 hours and meeting either of the criteria; (a) UA/NSTEMI with any of the following: transient ST elevation/depression with angina lasting for <20 min in the preceding 48 hours or persistent ST depression or T wave inversion associated with CPK/CPK MB rise of 3 × ULN during the preceding 48 hours or TIMI risk score of ≥4, (b) ST elevation MI (STEMI) >48 hours and <2 weeks, (c) multivessel PCI, (d) high risk lesion subsets with any of the following; long lesion >20mm or diffuse disease or ostial lesion or bifurcation or small vessels of diameter ≤2.75 mm and length ≥10 mm and (e) SVG lesions. Exclusion criteria were: STEMI >48 hours; pre treatment with streptokinase or other thrombolytic therapy within 48 hours; poorly controlled hypertension (BP>180/110 mmHg); active internal bleeding or bleeding diathesis, surgery, trauma, gastrointestinal or genitourinary tract bleeding within last 2 weeks; platelet count ≤100,000/mm³ or serum creatinine levels ≥2.5 mg/dL; cardiogenic shock upon admission; treatment with UFH within 6 hours (unless aPTT was ≤50 seconds or ACT ≤175 seconds), LMWH within 8 hours, bivalirudin within 24 hours, abciximab within 7 days or eptifibatide/tirofiban within 12 hours before the index. The patients were divided in two treatment strategies, Group I (bivalirudin, n=94, test drug) and Group II (heparin, n=109, standard drug).

4.2.2 Study Design and Clinical Endpoints:
It was a prospective, randomized, parallel group, open label, single centre study. The baseline characteristics like demographics, previous cardiac history, and angiographic parameters were assessed. Routine pathology tests were performed as per the local practice. Baseline CK and CK-MB measurements were done prior to the start of PCI and repeated at 12-24 hours post PCI. ACT at 10 min, end of the procedure and sheath removal time after PCI was determined. Bleeding events were recorded till
hospital discharge/ day 7 whichever was earlier. The in lab complications, peri procedural events and provisional use of GP IIb/IIIa inhibitors were recorded. Composite end point which included death, MI, revascularization, SAT, major & minor bleeding was recorded at day 7, day 30 & at 1 year. The final TIMI and TMP grade after PCI were assessed.

The primary endpoints were composite or individual incidences of death, MI, urgent revascularization (PCI or CABG), sub acute vessel occlusion or SAT and major/minor bleeding till day 7/hospital discharge, whichever was earlier. The secondary endpoints included day 30 and one year composite or individual incidences of death, MI, urgent revascularization, sub acute vessel occlusion or SAT. For composite analysis, all events were considered.

4.2.3 Study medication & dosage:

**Group I**

**Test Drug:** Bivalirudin was administered as a bolus dose of 0.75 mg/kg prior to start of PCI, followed immediately by the intravenous infusion of 1.75 mg/kg/h for the duration of PCI. The infusion of 0.25 mg/kg/hr was continued optionally up to 4 hours after PCI at Physician’s discretion. ACT was measured at 10 min after the bolus administration and at the end of the PCI procedure. After 10 min, an additional bolus dose of 0.3 mg/kg of bivalirudin was given if ACT remained <225 seconds. UFH or LMWH were not used immediately prior to or during the PCI procedure. If the infusion of GP IIb/IIIa inhibitors was continued post PCI, bivalirudin infusion was discontinued.

**Group II**

**Standard Drug:** Heparin bolus (5000 U/ml) of 70U/kg was administered prior to PCI. If ACT was between 150 to 199 seconds, additional 50U/kg heparin bolus was given. If ACT remained <200 seconds, additional 20 U/kg heparin bolus was given to maintain ACT >200 seconds.

❖ **Concomitant Medications**

1. **Recommended Concomitant Therapy**

   Aspirin ≥150mg and clopidogrel 600mg-900mg orally as a loading dose pre PCI or as per Physician’s discretion was recommended. Intravenous GP IIb/IIIa inhibitors administration was limited to provisional use. Post PCI aspirin ≥150mg orally
indefinitely and clopidogrel 75 mg for at least 30 days or continued as per the Physician’s discretion as per (ACC/AHA/ESC guidelines).

Provisional use of GP IIb/IIIa inhibitors

Indications for provisional GP IIb/IIIa inhibitors use included but were not restricted to, decreased TIMI flow (0 to 2) or slow reflow after 5 min of bolus administration, dissection with decreased flow, new or suspected thrombus, persistent residual stenosis, distal embolization, unplanned stenting, suboptimal stenting, side branch closure, abrupt closure, prolonged ischemia and clinical instability as per Physician’s discretion. The GP IIb/IIIa inhibitors like abciximab: 0.25 mg/kg bolus, 0.125µg/kg-min (max 10µg/min) X 12 hrs; or eptifibatide: 180µg/kg bolus, 2.0µg/kg-min X 18 hrs; or tirofiban: 10 µg/kg bolus over 3 min, followed by 0.15µg/kg/min for 16-18 hrs (RESTORE trial) or 25 µg/kg bolus over 3 min, followed by 0.15µg/kg/min for 16-18 hrs were administered. If GP IIb/IIIa inhibitors infusion was continued post PCI, simultaneous administration of bivalirudin infusion was stopped.

2. Contraindicated Concomitant Therapy:

Simultaneous administration of warfarin/UFH/LMWH was contraindicated. If patient have received UFH within 30 min (unless aPTT<50 seconds or ACT <175 seconds), LMWH within 8 hrs, bivalirudin within 24 hrs, abciximab within 7 days, eptifibatide or tirofiban within 12 hrs, such patients were not enrolled in study.

Table 4.1: Summarizes the Study Related Procedures

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Baseline</th>
<th>During PCI</th>
<th>Post PCI 12 hrs</th>
<th>Post PCI 24 hrs</th>
<th>Post PCI 07</th>
<th>Hospital Discharge/Day</th>
<th>30 day F/U</th>
<th>One year F/U</th>
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<td></td>
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<tr>
<td>TROPOIN-T</td>
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<td></td>
</tr>
<tr>
<td>ACT</td>
<td>X</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Outcome Events</td>
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<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
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</tr>
<tr>
<td>Bleeding Events</td>
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<td>X</td>
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<td>AE and SAE</td>
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</tbody>
</table>

Anuja Shah - 106 - L.M College of Pharmacy, Ahmedabad, India
4.3  EVALUATION OF SAFETY AND EFFICACY OF ABCIXIMAB (GP IIB/IIIA INHIBITOR) WITH STANDARD THERAPY IN MODERATE TO HIGH RISK ISCHEMIC HEART DISEASE PATIENTS PRESENTING WITH ACS AND UNDERGOING PCI

4.3.1  Study Population:

The patients with *de Novo* lesions of naive coronary vessels meeting the eligibility criteria were enrolled into the study which included (i) patients showing ischemic ST change in electrocardiogram among patients as well as refractory to drug treatment in resting phase or with recurrent angina pectoris (ii) post-infarction angina patients within 7 days from MI attack refractory to drug treatment and showing ischemic ST change in electrocardiogram (iii) acute Q-wave MI within 12 hours after the attack, which required direct intervention procedure (iv) acute Q-wave MI within 12 hours after the attack, which required another rescue intervention after failure to thrombolytic therapy. Exclusion criteria were concurrent anticoagulant therapy or a base line prothrombin time more than 1.2 times the control value or planned administration of anticoagulants, intravenous dextrans, poorly controlled hypertension (BP>180/110 mmHg); active internal bleeding or bleeding diathesis, surgery, trauma, gastrointestinal or genitourinary tract bleeding within last 4 weeks; cerebrovascular accident within the previous two years or a residual neurologic deficit, intracranial neoplasm, aneurysm, or arteriovenous malformation; history of vasculitis, known hemorrhagic diathesis, or active internal bleeding platelet count ≤100,000/mm³ or serum creatinine levels ≥2.5 mg/dL; cardiogenic shock upon admission. The patients were divided in two treatment strategies: Group I (abciximab and standard therapy, n=60) vs. Group II (standard therapy alone, n=60).

4.3.2  Study Design and Clinical Endpoints:

It was a prospective, randomized, parallel group, open label, single centre study. The baseline characteristics like demographics, previous cardiac history, and angiographic parameters were assessed and recorded. Routine pathology tests were performed as per the local practice. Baseline CK and CK-MB measurements were done prior to the start of PCI and repeated at 12-24 hours post PCI. Hemodynamic, biochemistry, electrocardiography, major/minor bleeding and thrombocytopenia and MACE (death, MI, urgent revascularization, SAT) were assessed on day 7 and day 30.
The primary efficacy endpoints were incidences of cardiac death, MI, urgent revascularization, sub acute vessel occlusion or SAT within 30 days of study therapy. The secondary safety parameters included occurrence of bleeding (major or minor), thrombocytopenia, change in Hb/Hct and any other AEs within 30 days of study therapy.

4.3.3 Study medication & dosage:

**Group I: Abciximab and Standard therapy**

**Abciximab:** Patients received abciximab 0.25 mg/kg i.v. bolus 10-60 min before the start of PCI, followed by a 0.125ug/kg/min (maximum, 10ug/min) infusion for 12 hours, while in unstable angina patients; abciximab 0.25 mg/kg intravenous bolus was followed by an 18 to 24-hour intravenous infusion of 10 pg/min, concluding one hour after the PCI.

**Standard therapy:** Heparin i.v. bolus (5000 U/ml) of 70U/kg was administered prior to PCI. If ACT is between 150 to 199 seconds, additional 50U/kg heparin i.v. bolus was given. If it still remains <200 seconds, additional 20 U/kg heparin i.v. bolus was given to maintain ACT >200 seconds.

**Group II: Standard therapy alone**

Heparin i.v. bolus (5000 U/ml) of 70U/kg was administered prior to PCI. If ACT is in between 150 to 199 seconds, additional 50U/kg heparin i.v. bolus was given. If it still remains <200 seconds, additional 20 U/kg heparin i.v. bolus was given to maintain ACT >200 seconds.

❖ Concomitant Medications

1. Recommended Concomitant Therapy:

   Aspirin ≥150mg and clopidogrel 600-900mg orally as a loading dose pre PCI or as per Physician’s discretion was recommended. Post PCI aspirin ≥150mg orally indefinitely and clopidogrel 75mg for atleast 30 days or continued as per the Physician’s discretion as per (ACC/AHA/ESC guidelines). The medications like nitrates, β-adrenergic receptor blocker, Ca Channel blocker, ACE inhibitor etc. were allowed.

2. Prohibited concomitant medications:

   Oral anticoagulants and dextrans (concomitant use of dextran prior to PCI or during PCI was contraindicated).
4.4 EVALUATION OF SAFETY AND EFFICACY OF ASPIRATION CATHETER FOLLOWED BY CONVENTIONAL STENTING WITH CONVENTIONAL STENTING ALONE IN ISCHEMIC HEART DISEASE PATIENTS PRESENTING WITH AMI AND UNDERGOING PCI

4.4.1 Study Population:

50 consecutive patients with de Novo lesions in mid or proximal segments of naive coronary vessels presenting with an AMI within 12 hours after the onset of symptoms and angiographically documented TIMI flow of 0 or 1 before wiring, visually estimated stenosis of $\geq70\%$ and estimated reference vessel diameter $\geq2.5$ mm and ECG showing ST-segment elevation of $\geq2$ mm in $\geq2$ contiguous leads were enrolled in the study. The patients were randomized in one of the following treatment strategies Group I [conventional stenting alone (PCI without use of aspiration catheter), standard group, n=25] and Group II (PCI with primary aspiration using aspiration catheter followed by conventional stenting, test group, n=25).

4.4.2 Study Design:

It was a prospective, randomized, open label, single centre study. The baseline characteristics, demographics, previous cardiac history, and angiographic parameters were assessed and recorded. An angiographic criteria of presence of visible distal embolization and improvement in myocardial blush grade was used to determine the end point of PCI, while ECG showing the rate of segment resolution $>50\%$ (60 min post procedure). The incidence of no-reflow/slow flow, side branch closure, and amount of thrombus load present, provisional use of GP IIb/IIIa inhibitors and composite end point which included death, MI, revascularization, SAT were recorded. The final TIMI and TMP grade after PCI was assessed. The total time consumed for the PCI was also recorded.

4.4.3 The Device:

The aspiration catheter is a commercially available device that has broadly been used in combination with the Medtronic Guidewire® (distal protection occlusion balloon) or as a separate device. Both devices are CE marked (authorized for marketing) devices.
and the combination of these devices provides vascular occlusion, and contain and aspirate embolic material while performing PTCA and/or stenting in vascular interventions prone to distal embolization.

It is a single-user design, dual lumen catheter, compatible with guidewire temporary occlusion and aspiration system. It has a distal radiopaque tip marker and proximal luer-lock port. The proximal luer-lock port is for connection of the aspiration line (supplied) and aspiration syringe (supplied). Also, an approximately sized syringe filled with an infusate may be attached to the aspiration line for the infusion of fluids (see figure: 4.1)

**Figure 4.1:** Aspiration Catheter

![Aspiration system Catheter](image)

**Table 4.2:** Features of Aspiration Catheter

<table>
<thead>
<tr>
<th>No.</th>
<th>Parts</th>
<th>Sub parts</th>
<th>Dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Catheter</td>
<td>Guidewire lumen</td>
<td>6-10 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total usable length</td>
<td>145 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distal radiomarker</td>
<td>1.5 mm from distal tip</td>
</tr>
<tr>
<td>2</td>
<td>Oblique tip</td>
<td>Lumen inner diameter</td>
<td>0.041”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lumen outer diameter</td>
<td>0.068”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max outer diameter at joint</td>
<td>0.054”</td>
</tr>
<tr>
<td>3</td>
<td>Aspiration system</td>
<td>Locking syringe</td>
<td>20 cc</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspiration rate</td>
<td>&gt;30 cc/min</td>
</tr>
</tbody>
</table>

**4.4.4 Procedure Description:**

(a) Preparation of Aspiration Catheter:
The aspiration catheter was supplied with an aspiration line and a locking aspiration syringe. The catheter and accessories from the package was removed and aspiration syringe was filled with approximately 5-10 ml of heparinized saline and attached the aspiration line and syringe to the catheter. The stopcock on the aspiration line was opened and the entire length of catheter was flushed using all of the heparinized saline contained in the aspiration syringe and thereafter the stopcock was closed and aspiration line was also verified for its closed position. The plunger of the aspiration syringe was retracted and pulled until it was locked at the fully extended position. The catheter was completely prepped and was ready for use. When using the catheter for fluid delivery the mentioned steps before was performed and it was then connected with infusion syringe of preferred volume or intravenous line to the aspiration line stopcock. The locking of aspiration syringe for fluid infusion was not recommended for use.

(b) Use of Catheter during a Guidewire Interventional Procedure

All the patients were preloaded with aspirin ≥150mg and clopidogrel 300 – 600mg before the procedure. The PCI procedure was done using femoral arterial approach. The aspiration was performed using the Export® catheter. The therapeutic catheter was withdrawn under fluoroscopy while leaving the guidewire catheter in place. The therapeutic catheter was removed from the wire and the entire exposed shaft was wiped using gauze soaked with heparinized saline. The prepped catheter was loaded over and advanced on the guidewire catheter to the tip of the guiding catheter. The catheter was advanced under fluoroscopy and the distal tip marker was positioned proximal to the guidewire radiopaque balloon marker. The advancement of the catheter can be stopped if resistance has encountered. Alignment of the radiopaque marker of the catheter with the guidewire radiopaque marker should not be attempted. Aspiration was started by opening the stopcock on the aspiration line. The catheter was slowly retracted towards the guiding catheter and blood was entering in the aspiration syringe until the entire vacuum has gone (or the aspiration syringe is filled). After completing the aspiration process, aspiration line stopcock was turned to close off the aspiration syringe. The catheter was removed by withdrawing slowly and retracting the catheter. If require, the Touty Borst of the RHV could be loosen to allow easy withdrawal of the distal shaft. Thereafter the catheter was
removed and standard hospital practice for management of the insertion site was followed.

4.4.5 Angiographic evaluation:
Coronary angiograms were assessed by two independent cardiologists who were unaware of the study group, cardiac history and risk factors of the patients so as to avoid the personal bias. Angiographic distal embolization and presence of thrombus was assessed. The degree of perfusion was evaluated according to Thrombolysis in Myocardial Ischemia (TIMI) criteria. Good collateral flow was defined as Grade 2 or Grade 3.

4.4.6 Concomitant medications:
Aspirin ≥150mg and clopidogrel 300 – 600mg loading dose before the procedure was done. The patients pretreated with lytic therapy or GP IIb/IIIa inhibitors were not randomized for the study, however after cathlab admission use of lytic therapy or GP IIb/IIIa inhibitors was as per cardiologist’s discretion.

Post PCI aspirin ≥150mg orally indefinitely and clopidogrel 75 mg for atleast 30 days or continued as per the Physician’s discretion (as per ACC/AHA/ESC guidelines). The medications like nitrates, B-adrenergic receptor blocker, Ca++ Channel blocker, ACE inhibitor were allowed.

4.4.7 Electrocardiogram Interpretation:
ECG was interpreted differently by two independent cardiologists unaware of the study group, cardiac history and risk factors of the patients to avoid the personal bias. The ECGs were taken during pre procedure, post procedure, 60 min after procedure and 24 hr after procedure. The improvement in ECG was defined as rate of ST segment resolution >50% and achievement of baseline ECG (normal).

4.4.8 Procedural Time:
The total procedural time was recorded which consists of the time period from first cine of guide catheter engagement till last cine of TIMI flow achieved.
4.4.9 **Clinical Endpoints:**

The primary endpoint of this study was to evaluate the rate of ST segment resolution >50% (60 min post procedure) and improvement in myocardial blush grade III because both the markers have been recognized as surrogate endpoints for long-term mortality rates in patients with acute MI (Van’t et al, 1998, Hoffmann et al, 2003, Henriques et al, 2003, Gibson et al, 2002, Poli et al, 2002) and achievement of clinical success. Secondary endpoints was to evaluate the (i) clinical performance of the aspiration catheter which included the immediate technical device success, angiographic success and procedural success, (ii) achievement of TIMI III flow an important indicator for rapid restoration of epicardial flow and has been recognized as important predictor of clinical and angiographic outcome in AMI (Gibson et al, 2002), (iii) angiographic evidence of distal embolization in patients treated with primary angioplasty (Van’t et al 1998, Hoffmann et al 2003, Henriques et al 2003, Gibson et al 2002, Poli et al 2002) (iv) provisional use of GP IIb/IIIa inhibitors, rate of rescue medication use, rate of aspiration catheter use or distal protection device which provides success of treatment, and (v) MACE such as death, ReMI, TLR, TVR, emergent PCI or CABG were assessed after the procedure, day 30 and on one year.
4.5 STATISTICAL ANALYSIS:

Independent variables included were age, sex; risk factors and medical history are expressed as value or percentages and were compared by Chi Square ($\chi^2$) test. Continuous variables like changes in lipoproteins levels from baseline to treatment phase (within the group) were expressed as mean±SD (standard deviation) and were compared using two sample paired t-test. Continuous variables (between the groups) were expressed as mean±SD (standard deviation) and were compared using unpaired Student’s t-test (baseline parameters). P value less than 0.05 was considered to be statistically significant.

4.6 DEFINITIONS OF CLINICAL ENDPOINTS:

Death: Deaths were classified as cardiovascular or non cardiovascular. All deaths with known cardiovascular cause or unknown cause were classified as cardiovascular. Within cardiovascular deaths, a hemorrhagic death was clearly identified. Deaths documented for non-cardiovascular cause (e.g. cancer) was classified as non cardiovascular.

Myocardial Infarction (MI/AMI): MI was defined (i) Typical rise and fall of biochemical markers of myocardial necrosis (including troponin, CK-MB, CK) to greater than 2× ULN (of if markers already elevated, greater than 50% of the lowest recovery enzyme level from the index infarction) with atleast one of the following: (a) ischemic symptoms, (b) development of pathological Q wave on the ECG, (c) ECG changes indicative of ischemia (ST segment elevation or depression) and (d) coronary artery intervention (ii) pathological findings of an acute MI (according to ACC clinical data standards).

Urgent revascularization: It was defined as any urgent surgical or repeat percutaneous coronary revascularization in the patient apart from the index PCI.

Sub Acute Thrombosis or Sub acute occlusion: It was defined as angiographic thrombus or sub acute closure within the stented vessel at the time of the clinically driven angiographic re-study for documented ischemia (chest pain or ECG changes).
Major bleeding: It was defined as clinically overt bleeding with at least one of the following criteria; (i) fatal or, (ii) symptomatic intracranial hemorrhage or, (iii) retroperitoneal hemorrhage or, (iv) intraocular hemorrhage leading to significant vision loss, or (v) any clinically significant overt sign of hemorrhage that is associated with a fall in Hb >3 g/dl or requiring transfusion of two or more units red blood cells or equivalent of whole blood.

Minor bleeding: It was defined as spontaneous bleeding like gross hematuria or hematemesis -- spontaneous or iatrogenic bleeding observed with decreased in Hb >3 g/dl (or hematocrit ≥10%).

Thrombocytopenia: It was defined as decrease in platelet count >25% when compared to baseline count and platelet count <100,000.

Electrocardiographic assessment: Rate of ST segment resolution: ST-T Segment normalization was classified by means of comparison of the elevation at baseline with the elevation post-procedure. Extent of ST-segment elevation resolution was described Schroder et al 1994:
Complete resolution: ≥ 70% normalization
Partial resolution: 30%-70% normalization
No resolution: < 30% normalization

Clinical success: A procedure success without death, Target Lesion Revascularization (CABG or PTCA) or Myocardial Infarction before hospital discharge

Device success: Device success was defined as successful crossing of the occlusion by aspiration catheter. In proximal direction keeping negative pressure and to contain and aspirate embolic material (thrombus/debris) while performing a stenting procedure.

Angiographic success: Angiographic success was defined as residual lumen diameter stenosis <20% and TIMI flow grade III after the intervention
**Procedural success:** Procedural success was defined as angiographic success without the occurrence any periprocedural adverse events.

**Distal embolization:** It was defined as an abrupt cut-off in one or more branches of target vessel.

**Thrombus:** It was defined as a filling defect seen in multiple projections surrounded by contrast and in the absence of calcification.

**Calcification:** It was defined as readily apparent radiopacities within the vascular wall at the site of the stenosis and classified as none/mild, moderate (radiopacities noted only during the cardiac cycle before contrast injection) and severe (radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen).

**Assessment of blood flow:**

1. **Thrombolysis in Myocardial Infarction (TIMI) flow grades:**

   The culprit lesion was determined by its anatomical location, its perfusion characteristics according to Thrombolysis in Myocardial Infarction (TIMI) classification for flow through the infarct related vessel (Sutsch et al 2000):

   - **TIMI flow 0** was assigned if there was no antegrade flow beyond the point of occlusion or there was no visible filling of any collateral channels.
   - **TIMI flow I** was designated if there was penetration without perfusion or minor perfusion i.e. contrast material passes beyond area of obstruction, but “hangs up” and fails to opacify entire coronary bed distal to obstruction for duration of cine angiographic filming sequence. There was filling by means of collateral channels of side branches of the vessel but without any dye reaching the epicardial segment of that vessel.
   - **TIMI II flow** was designated when there was partial or mild perfusion. Contrast material passes across obstruction or its rate of clearance from distal bed (or both) is perceptibly slower than its entry into or clearance from distal bed (or both) comparable areas not perfused by previously occluded vessels. Partial filling occurs via collateral channels of the epicardial segment of the vessel.
TIMI III flow was assigned for complete and good perfusion as visualized by complete filling of the vessel. Antegrade flow into bed distal to obstruction occurs as promptly as antegrade flow into bed proximal to obstruction and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or opposite artery.

(2) Myocardial blush grade / TIMI myocardial perfusion (TMP):

Perfusion can be defined as tissue blood flow at the capillary level. Perfusion of the myocardium can be categorized using the TIMI myocardial perfusion (TMP) classification described (Gibson et al 2000):

TMP grade 0 was assigned when there was failure of the dye to enter the microvasculature. There was either minimal or no ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit artery, indicating lack of tissue-level perfusion.

TMP grade 1 was assigned when the dye slowly enters but fails to exit the microvasculature. There is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature and dye staining is present on the next injection.

TMP grade 2 was considered when there was delayed entry and exit of dye from the microvasculature. There is the ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (i.e., dye is strongly persistent after 3 cardiac cycles of the washout phase and either does not or only minimally diminishes in intensity during washout).

TMP grade 3 was designated when there was normal entry and exit of dye from the microvasculature. There is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that clears normally and is either gone or only mildly/moderately persistent after 3 cardiac cycles of the washout phase, similar to that in an uninvolved artery. Blush that is of only mild intensity throughout the washout phase but fades minimally is also classified as grade 3.

Major Adverse Cardiac Events (MACE): It was defined as individual or composite event of death, (re)infarction (Q- and non Q wave), emergent bypass surgery, and target
lesion revascularization [coronary artery bypass surgery (CABG), or repeat percutaneous transluminal coronary angioplasty (PTCA)] and cerebrovascular accidents (CVA; disabling stroke).

**Stent thrombosis:** Defined as angiographic thrombus or subacute closure within the stented vessels at the time of the clinically driven angiographic restudy for documented ischemia (chest pain and ECG changes). Any death not attributed to a non cardiac cause within the first 30 days was considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.

**Target Lesion Revascularization (TLR):** TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel.

**Clinically-driven:** Revascularization are those in which the patient had a positive functional study, ischemic ECG changes at rest in a distribution consistent with the target vessel, or ischemic symptoms, and in-lesion diameter stenosis ≥70% (by QCA) in the absence of the above mentioned ischemic signs or symptoms was also considered clinically driven. In the absence of QCA data for relevant follow-up angiograms, the clinical need for revascularization was adjudicated using the presence or absence of ischemic signs and symptoms.

**Target Vessel Failure (TVF):** Target vessel revascularization (defined below), MI, or death that can not be clearly attributed to a vessel other than the target vessel.

**Target Vessel Revascularization (TVR):** Any PCI of the target vessel or bypass surgery of the target vessel (clinically driven or non-clinically driven, see TLR).

**Target Vessel Thrombosis/Occlusion:** All stents/target vessels with angiographically demonstrated occlusion/thrombosis were classified as:

- Early – occurring between removal of the guiding catheter until 30 days
- Late – occurring after 30 days
- Associated with symptoms – Unstable angina ≥Braunwald Class 1 or myocardial infarctions, Q-or non Q wave).
• Not associated with symptoms – as described above

**De Novo Lesion:** It was defined as a coronary lesion not previously treated.

**Killip Classification:** The severity of acute myocardial infarction was determined according to the classification (Killip et al, 1967) into four mutually exclusive levels:

1. Class 1: no signs of congestive heart failure (no rales or crackles)
2. Class 2: rales (crackles) in one half or less of both lung fields.
3. Class 3: rales (crackles) in more than one half of both lung fields (pulmonary edema).
4. Class 4: cardiogenic shock (systolic blood pressure of ≤90 mmHg; decreased urine output, cold, clammy skin; cyanosis; or mental obtundation).