"An idea that is developed and put into action is more important than an idea that exists only as an idea."

Introduction
INRODUCTION

In 2005, the World Health Organization (WHO) reported that cardiovascular diseases (CVDs) caused 17.5 million (30%) of the 58 million deaths globally (WHO, 2005). CVD such as ischemic heart disease (IHD) (also called as CAD/CHD) and strokes are the largest causes of death in developing countries and are one of the main contributors to disease burden (Gaziano et al 2006). Coronary artery disease (CAD) is a major cause of death all over the world. It is often premature and follows a malignant course (Enas et al 1995). It is responsible for major disability in both the developed and developing countries. CVD in India cause 3 million deaths in a year and accounting for 25% of all mortality (Mukherjee 1995). IHD is the leading cause of death in India (Reddy 1993, Reddy et al 1998, Bulatao et al 1990). Moreover, research on Indian Asians living abroad indicates a 40% higher risk of IHD mortality than that for Europeans (Balarajan 1996). By 2010, 60% of the world’s patients with heart disease will be in India (Gaziano et al 2006). Age standardized CVD death rates (per 100,000) in middle-aged (30–69 years) are low in developed countries such as Canada (120) and Britain (180) and high in developing countries Brazil (320), China (280), Pakistan (400), Nigeria (410), Russia (680) and India (405) (WHO, 2005). The present burden of CVD related deaths and quality of life indicates a need for effective prevention as well as therapeutic management of these patients.

IHD is an umbrella term having spectrum of condition called as CAD/CHD, or atherosclerotic heart disease, is the end result of the accumulation of atheromatous plaques within the walls of the arteries that supply the myocardium (the muscle of the heart) with oxygen and nutrients. The acute coronary syndromes (ACS), a subset of CAD is a group of clinical conditions which included unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), ST segment elevation MI (STEMI) and ischemic death which shares common pathophysiologic process. Coronary thrombosis is a pivotal event in the pathogenesis of ACS. Plaque rupture is an important contributor resulting in platelet adhesion and aggregation as well as tissue factor and coagulation factor activation at the site of intracoronary thrombus formation. Platelet function is influenced by thrombus. Hence, thrombin generation is most important both in chronic
progression of atherosclerotic disease and its conversion to acute events. An early invasive strategy for patients with moderate or high risk ACS, consisting of angiography followed by PCI or coronary artery bypass grafting (CABG) or medical management, which results in higher rates of event free survival than does conservative care (Mehta et al 2005) and is recommended by American Heart Association, American College of Cardiology, and European society of Cardiology (Braunwald et al 2006, Braunwald et al 2002 and Bertrand et al 2002).

Studies have confirmed that lowering low density lipoproteins (LDL), very low density lipoproteins (VLDL) and VLDL remnants significant improves the risks for CVD and have demonstrated the protective benefits on high density lipoprotein (HDL) (Mukhtar et al 2005). After a diet and life-style changes, various classes that target to reduce the total cholesterol, LDL cholesterol and to improve the HDL cholesterol level are HMG-CoA reductase inhibitors, bile acid sequestrants, nicotinic acid and fibric acid derivatives which slows down the progression of CAD to plaque and thrombus formation. It has also been clearly demonstrated over the last 20 years that antiplatelet/antithrombotic drugs played a major role for the management of ACSs (Bertrand et al 2006). The three pharmacologic agents targeting on coronary thrombus includes; a) antiplatelet agents like cyclo-oxygenase 1 inhibitor (aspirin), thienopyridines (clopidogrel) and GPIIb/IIIa inhibitors (abciximab, eptifibatide and tirofiban); b) antithrombin inhibitors such as UFH, LMWH, and bivalirudin; and c) plasminogen activators such as t-PA, r-PA, SK, TNK-tPA are the drugs recommended for patients in whom an invasive strategy is chosen. The current management strategies of IHD patients presenting with ACS includes use of various drugs (statins, antiplatelet, antithrombin agents, etc.) as well as interventional procedures such as percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG) involving use of various medical devices like stents, etc. The study encompassed in the present thesis aims to evaluate the subsets of different drug classes that prevent the process of atherosclerosis (preventive management); decreases platelet aggregation and thrombus formation (therapeutic management during PCI); and to study a medical device that removes the thrombus (during PCI) in IHD patients.
Atherosclerosis and its complications are the leading causes of mortality amongst the men and women worldwide. Central to the pathogenesis of atherosclerosis is a chronic state of dyslipoproteinaemia and inflammation, which encourages cholesterol and plaque formation within arterial walls, exacerbated by hypertension, tobacco use and diabetes. The process is mediated through a variety of lipoprotein subclasses including LDL and VLDL, which transport cholesterol and TG to peripheral tissues and are responsible for the formation of lipid-rich, unstable atheromatous plaques that are the basis of atherosclerosis (Mukhtar et al 2005). An adverse lipid profile is identified among the several risk factors that could account for atherosclerosis and progression of CAD. Elevated levels of LDL cholesterol have been recognized as the most important risk factor for CAD. Various regression studies have provided clinical evidence that aggressive lipid lowering can induce atherosclerotic lesion stabilization or even regression and thereby reduce clinical CAD events (Gotto 1995). Thus, the management of cholesterol can reduce the burden of CAD diseases (Ansell 2002). Statins are a class of drug that are potent and safe and effectively lower LDL levels. Statins have been shown to stabilize unstable plaques, improves vascular relaxation and promote new vessel formation (Auer et al 2002). Statins inhibit the rate limiting enzyme in cholesterol production and hence, up-regulate hepatic LDL receptors increasing the removal of apolipoprotein B (Apo B) containing lipoproteins from plasma. The effectiveness of statins has been demonstrated in many clinical trials (Klotz 2003, Brosseau 2003, Athyros et al 2002). Available worldwide are atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. The increasing need for more aggressive lipid lowering has fuelled a need for more efficacious statins. Pitavastatin is a new highly effective statin and is reported to be more effective in LDL cholesterol reduction than pravastatin, simvastatin or atorvastatin (Flores 2002, Saito et al 2002, Iglesias et al 2003) with a longer duration of action and similar or reduced potential for drug interactions. In a short-term double blind three group, parallel study in primary hypercholesterolemia compared the efficacy of pitavastatin at the doses of 1, 2 and 4 mg over 12 weeks followed a 4-week placebo run in phase and followed by 4-week placebo run-out has been reported to produce reduction in TC, LDL cholesterol and TGs. It also showed raise in HDL cholesterol (Saito et al 2002). In another short-term study, in individuals with
heterozygous familial hypercholesterolemia, pitavastatin at 2mg/day for 8 weeks has been reported to significantly reduce total and LDL cholesterol by 30 and 42% respectively (baseline levels total cholesterol 8.8±1.38 mmol/l, LDL cholesterol 6.81±1.52 mmol/l). Further increase in dose to 4mg/day for another 8 weeks reported to further reduce in total cholesterol and LDL levels by a 6% with 37 and 48% respectively. The drop in LDL-cholesterol levels were comparable to those produced by atorvastatin 20 and 40 mg daily, with the 6% additional fall in LDL-cholesterol levels with the doubling of statin doses (McKenney et al 2003). Mean LDL-cholesterol levels achieved (3.55±0.85 mmol/l) were close to the target levels set by the NCEP ATP III guidelines for individuals with two or more risk factors, 3.4 mmol/l. TG levels were reduced by 15% and 23% significant at both doses. Significant reductions in Apo B, CII, CIII and E were noted (41%, 27%, 19% and 37% from baseline, respectively) while levels of Apo A1 and Apo A11 rose by 9.5% and 5.8% (Kajinami et al 2000, Kajinami et al 2000). Studies on pitavastatin in Indian subset of patients are scanty. Thus, we have considered it worthwhile to study the efficacy and safety of the pitavastatin with atorvastatin in hyperlipidemic patients.

Thrombin is a key enzyme of the coagulation cascade, as it controls the ultimate step, the conversion of fluid-phase fibrinogen into fibrin, which is scaffold of the clot. Furthermore, thrombin sustains the clotting process by two mechanisms: amplification of its own production by activating the intrinsic pathway, particularly factors XI, IX, VIII, and X and platelet activation. Thrombin binds to fibrin, fibrin degradation products, as well as sub endothelial matrix and remains active once bound (Collet et al 2007). The current mainstays of anticoagulation treatment are unfractionated heparin (UFH), which is an indirect thrombin inhibitor, and coumarins, such as warfarin, which modulate the synthesis of vitamin K-dependent proteins. Traditionally, UFH is the standard of adjunctive antithrombin therapy during percutaneous coronary interventions (PCI). However, UFH holds some limitations of variable efficacy and stability, mainly due to poor bioavailability, non-specific protein binding, neutralization by platelet factor-4, and a lack of efficacy on fibrin-bound thrombin results in difficult to manage effects on coagulation, the need for repeated monitoring of coagulation, the narrow therapeutic
window, the potential induction of platelet activation, and the risk of thrombocytopenia. Moreover, UFH exhibits prothrombotic properties related to a poor control of von Willebrand factor release, as well as platelet activation of the GP IIb/IIIa receptor and thrombin generation rebound after discontinuation (Montalescot et al 2003, Montalescot et al 2000, Montalescot et al 1998, Xiao et al 1998). Bivalirudin is a 20 amino acid bivalent peptide that inhibits thrombin directly and has several advantages over heparin (Maraganore 1993). These advantages include, high specificity and potency for thrombin inhibition; a lack of dependence on antithrombin III for anticoagulant activity; the ability to inactivate both clot-bound and free thrombin, and a lack of aggregatory effects on platelets. Bivalirudin has been evaluated in several clinical trials for UA, AMI, and PCI indications (Maraganore 1993, Topol et al 1993, Fuchs et al 1995, Lidon et al 1993, Bittl et al 1995, Theroux et al 1995, White et al 1997, Cannon et al 1993). In the randomized study, The Hirulog and Early Reperfusion or Occlusion (HERO), bivalirudin vs. heparin in patients receiving fibrinolytic therapy for AMI the treatment of re-infarction by PCI, using bivalirudin within 12 h was reported to lower 30 day mortality (White et al 1997). The prospective, multicenter, open label study, Anticoagulant Therapy with Bivalirudin to Assist in the Performance of PCI in Patients with Heparin-induced Thrombocytopenia (HIT) (ATBAT), concluded that the use of bivalirudin in patients with HIT who require coronary intervention is safe and effective anticoagulant (Mahaffey et al 2003). The results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET) reported significant reduction in the combined rates of death, MI, revascularization, and major hemorrhagic in patients with bivalirudin with provisional abciximab vs. low-dose heparin and abciximab during percutaneous coronary revascularization (Lincoff et al 2002). In the prospective, multicenter study, for the effectiveness of the concomitant use of bivalirudin and Drug-Eluting Stents (ADEST) was reported to low rates of major adverse cardiac events (MACE), stent thrombosis and major bleeding in the patients undergoing PCI (Dangas et al 2005). The single arm, multicenter, open label study, Bivalirudin in Acute Myocardial Infarction patients (BIAMI) reported significant reduction in bleeding, composite end points and thrombocytopenia. The Randomized Evaluation in PCI Linking Angiomax to reduced Clinical Events (REPLACE)-I trial in patients undergoing PCI demonstrated that
bivalirudin reduced the triple ischemic end-point of death, MI and urgent revascularization at 48 hours as compared to heparin (Lincoff et al 2004). The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial with bivalirudin in moderate-high-risk ACS patients showed an improved in therapeutic ratio with reduced ischemic events and reduced bleeding complications during PCI (Stone et al 2007). A recent analysis in a subgroup of REPLACE-2 population suggested that bivalirudin and provision GP IIb/IIIa inhibitors use compared with heparin and routine GP IIb/IIIa inhibitors regimen showed similar rates of ischemic complications, reduced bleeding and substantial cost savings to both hospitals and the healthcare system (Lincoff et al 2003, Lincoff et al 2004). In the prospective, randomized comparison of bivalirudin vs. heparin plus GP IIb/IIa inhibitors during primary angioplasty in Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial reported reduction in the composite endpoint of death, MI, target vessel revascularization, stroke and major bleeding at 30 days. Although reported studies prove that bivalirudin is safer, cost-effective (Bakhai et al 2006) and convenient agent in the spectrum of clinical scenarios. There is a scanty data about its utility as primary anticoagulant for PCI especially in Indian patients with a moderate to high-risk. We conducted the study with the aim to evaluate the efficacy and safety of bivalirudin and compared with heparin as an adjunct to PCI in moderate to high-risk IHD patients presenting with ACS and undergoing PCI with provisional GP IIb/IIIa inhibitors use.

Antiplatelet and antithrombotic therapies have been the corner stone for the treatment of patients with ACS. New strategies for preventing ischemic complications during percutaneous coronary revascularization have focused on the platelet surface membrane GP IIb/IIa receptor (EPILOG investigators 1997). Consistently observed benefits with GP IIb/IIa inhibitors as an adjunct to aspirin and antithrombotic therapy in large randomized clinical trials have also led to their therapeutic use in patient undergoing PCI. Platelet aggregation depends on activation of the GP IIb/IIa receptor, which is the final common pathway of platelet activation (Lefkovits et al 1995). GP IIb/IIa receptors are expressed on the surface of activated platelets. They link to fibrinogen to form bridges between activated platelets, leading to the formation of
platelet thrombi (Bertrand et al 2006). Inhibition of platelet activation by aspirin and heparin provides benefit in ACS but does not always ensure optimal outcomes if platelet inhibition is insufficient (Theroux et al 1988). The GP IIb/IIIa inhibitors are new and promising. GP IIb/IIIa receptor inhibitor is efficacious as adjunctive therapy in the treatment of ACS and PCI and improves outcomes when administered with aspirin and antithrombin agents (The EPIC investigators 1994, The EPILOG investigators 1997, The IMPACT-II investigators 1997, The PURSUIT trial investigators 1998, The RESTORE investigators 1997, The PRISM-PLUS study investigators 1998). GP IIb/IIIa inhibitors have been shown to inhibit platelets, increase resolution of coronary thrombus, improve coronary flow, enhance myocardial perfusion (Neumann et al 1998) and prevent early recurrent ischemic events (MI, refractory ischemia or urgent revascularization) (The EPISTENT investigators 1998, The EPIC investigators 1994, Topol et al 1997, Neumann et al 1998, The IMPACT-II investigators 1997). Direct inhibitors of the GP IIb/IIIa receptors have been developed and have been tested in various conditions where platelet activation plays a major role, particularly, in patients undergoing PCI, patients admitted for ACS and patients receiving thrombolytic therapy for AMI (Bertrand et al 2006). Abciximab, eptifibatide and tirofiban are the three GP IIb/IIIa inhibitors currently approved by the US FDA for therapeutic use in ACS and/or adjunctive therapy to PCI (Linc-off et al 1997). In addition ACC/AHA guidelines for the management of PCI and ESC recommendation for ACS both indicate the use of GP IIb/IIIa inhibitor, especially in high risk patients (Anderson et al 2007). Abciximab is approved for use in patients with refractory unstable angina in whom PCI is planned within 24 h. Abciximab, the Fab fragment of the chimeric antibody to the GP IIb/IIIa receptor (and to a broader group of integrin) is able to block platelet aggregation as well as inhibit thrombin generation of tissue factor by 3,4β3 (Simon et al 1997, Revert-er et al 1996). The results from the Evaluation of Platelet IIb/IIIa Inhibitor for STENTing (EPISTENT) in PCI reported that the addition of abciximab led to a >50% reduction in death, MI and urgent revascularization (The EPISTENT investigators 1998). In the randomized, double blind, placebo-controlled trial Evaluation of IIb/IIIa platelet receptor inhibitor abciximab in Preventing Ischemic Complications (EPIC) trial in ACS patients with PCI at high risk for abrupt vessel closure reported reduction in death, MI, urgent revascularization and
mortality. In the prospective, randomized, double blind, placebo-controlled Evaluation of PTCA to improve long term outcome of GP IIb/IIIa receptor blockade (EPILOG) in ACS patients with PCI reported reduce death and myocardial infarction (The EPILOG investigators 1997). The results of ISAR-REACT 2 Randomized Trial reported that abciximab leads to the reduction in the risk of adverse events in patients with non-ST-segment elevation ACS and undergoing PCI after pretreatment with 600 mg of clopidogrel. The benefits provided by abciximab appear to be confined to patients presenting with an elevated troponin level (Kastrati et al 2006). We have evaluated the efficacy and safety of abciximab in moderate to high risk IHD patients presenting with ACS and undergoing PCI so as to prevent ischemic cardiac complications.

DeWood and colleagues in 1980 demonstrated the presence of thrombus in the infarct-related artery of 88% of patients undergoing coronary artery angiography within first four hours of AMI. This landmark study has initiated a shift in the treatment and management of AMI with the use of thrombolytic agents and later on with PCI for the prompt restoration of epicardial coronary artery blood flow. A number of randomized clinical studies have shown that PCI is superior to thrombolytic therapy in the treatment of AMI in terms of restoration of normal coronary blood flow (DeWood et al 1980). However, PCI is associated with lower rates of recurrent ischemia, stroke, reinfarction and death. The use of stents in PCI has been shown to provide further improvements in patient outcomes, including post-intervention minimal lumen diameter, restenosis rates, and the occurrence of ischemia, stroke, reinfarction and death (Grines et al 1999, Suryapranata et al 1998, Kastrati et al 2000). However, improvements in coronary artery flow do not always lead to the anticipated improvements in myocardial perfusion. In patients where adequate myocardial reperfusion is not achieved, poor functional recovery is generally observed. The failure to achieve adequate reperfusion may result from necrosis of myocytes and microvascular network arising as a consequence of either ischemia or the embolization of plaque or thrombus material from the target lesion (Kloner et al 1974, Topol et al 2000, Henriques et al 2002, Ito et al 1996, Stone et al 2002, Antoniucci et al 2004). Distal embolization has been shown to occur in approximately 15% (Ito et al 1996) of post-angioplasty patients and has been associated
with reduced myocardial reperfusion, more extensive myocardial damage and a poor prognosis (Topol et al 2000, Henriques et al 2002). Distal embolization of particulate matter, including plaque debris and thrombus complicate PCI that often results in diminished blood flow to the distal vascular bed and is associated with periprocedural end-organ ischemia and infarction, as demonstrated by perfusion defects and serum cardiac enzymes elevation (Califf et al 1998, Koch et al 1999). Periprocedural myocardial infarction (MI) is associated with a worse prognosis, particularly when it’s large MI. Distal embolization of large particles at the time of balloon inflation or stent deployment may obstruct large, epicardial vessels, but the scope of the problem includes microvascular obstruction due to very small particles, as little as 15-100 microns, that may result in microinfarcts and left ventricular dysfunction (Hori et al 1991). It is likely that mechanical microvascular obstruction is commonly aggravated by secondary spasm and edema due to release of humoral agonists by platelets, endothelial injury and dysfunction. Limited therapeutic success has been reported from observational studies involving the use of calcium channel blockers, adenosine and sodium nitroprusside (Piana et al 1994). However, the success rate of these medical interventions is most commonly defined by angiographic resolution of the “no-reflow” phenomenon an acute reduction in coronary flow less than thrombolysis in myocardial infarction (TIMI) in the absence of dissection, thrombus, spasm, or high grade residual stenosis at the original target lesion. A beneficial effect on hard clinical endpoints has been more difficult to prove (Fasseas et al 2001). Recent development to improve percutaneous reperfusion strategies includes transluminal extraction atherectomy, excimer laser coronary angioplasty (ELCA), angiojet thrombectomy, coronary ultrasound thrombolysis (CUT) and aspiration thrombectomy (ICAT). A number of filter devices utilize an expandable filter mounted on the angioplasty guidewire to facilitate entrapment of particles and safe removal. The Parod Anti-emboli system™ is an example of a catheter occlusion device that establishes protection by reversing blood flow in the target vessel (Fasseas et al 2001). A number of distal protection devices are under development. In an effort to reduce complications such as distal embolization and no-reflow, a new catheter system Percusurge Guard Wire™ temporary occlusion and aspiration system distal protection device has been developed. Aspiration catheter used in our study is a device which is a
component of Percusurge Guard Wire™ consists of only aspiration system. Aspiration catheter is a commercially available device that has been used in combination with distal protection occlusion balloon or as a separate device. Both devices are CE marked devices provides vascular occlusion, and contain and aspirate embolic material while performing percutaneous transluminal angioplasty (PTCA) and/or stenting in vascular interventions prone to distal embolization. Clinical data on the use of aspiration catheter in patients with AMI is less. Clinical studies in patients with AMI have shown that stenting in combination with these distal protection and aspiration devices is safe and effective in terms of retrieving debris, improvement in TIMI flow post-procedure and post-procedural myocardial blush (Huang et al 2003, Orrego et al 2003, Stone et al 2005, Kusuyama et al 2004, Nakamura et al 2004, Chen et al 2004, Taguchi et al 2005). The EMERALD study is one of the first large randomized studies (that included over 500 AMI patients) in which stenting with distal protection (using the before mentioned devices) was compared to conventional stenting. Although in EMERALD study this device effectively retrieved embolic debris, it failed to show improved micro vascular flow, greater reperfusion success, reduced infarction size, or enhanced event-free survival. The REMEDIA investigators reported significant resolution in ST segment after primary aspiration than conventional stenting. However, the incidence of MACE was identical. TAPAS study (Svilaas et al 2008) reported the primary aspiration followed by conventional stenting resulted in better reperfusion and clinical outcome than conventional stenting (PCI) alone. Thus, results are variable with this device. We have conducted the study with aspiration catheter followed by conventional stenting in IHD patients presenting AMI with the aim to find out whether the use of primary aspiration could reduce the complication rate of PCI, by allowing removal of embolic debris.
Overall objectives of the study

⇒ Preventive therapy –
   ▪ To evaluate efficacy and safety of pitavastatin and compare with atorvastatin in hyperlipidemic patients

⇒ Medical management (treatment) –
   ▪ To evaluate safety and efficacy of bivalirudin (antithrombin agent) and compare with heparin as an adjunct therapy in moderate to high-risk IHD patients presenting with ACS and undergoing PCI
   ▪ To evaluate safety and efficacy of abciximab (GP IIb/IIIa inhibitor) plus standard therapy and compare with standard therapy in moderate to high-risk IHD patients presenting with ACS and undergoing PCI

⇒ Intervention (treatment) –
   ▪ To evaluate safety and efficacy of aspiration catheter followed by conventional stenting and compare with conventional stenting alone in IHD patients presenting with AMI and undergoing PCI