Imagination and knowledge with proper effort leads to the path of achievement and success!

Discussion
6: DISCUSSION

IHD is one of the mostly studied and has shared its wider horizon in the arena of medicine development. As a result, many interventions exist with strong evidence for significant reductions in morbidity and mortality associated with IHD. In spite of this contribution, disease still remains the biggest challenge with growing rate of incidence and prevalence globally. It still needs the better treatment strategies and management to annihilate the rising disease burden. Our study evaluated drugs and devices in the preventive and therapeutic management of patients with IHD presenting with ACS.

In our first subset of study which was preventive management of IHD, showed long term use of pitavastatin have significant efficacy and comparative safety with atorvastatin in hyperlipidemic patients. Use of pitavastatin showed significant reduction of LDL-C on week 24 (28% vs. 23%, \(p<0.001\)) and week 52 (45% vs. 33%, \(p<0.001\)) from baseline. There was significant reduction in Apo B levels on week 24 (22% vs. 15%, \(p<0.001\)) and week 52 (36% vs. 31%, \(p<0.05\)) from baseline. Pitavastatin treated patients showed significant improvement in the TC, TG and HDL-C levels on week 52 from baseline. No elevations in hepatic enzyme, CK, hsCRP and urine myoglobin levels were recorded till the end of treatment period. No adverse events were reported during 52 weeks of treatment period in 50 patients.

Our study reported that pitavastatin (2mg/d) showed percent reduction of LDL-C (45%) and TC (36%) on week 52 from baseline which was in line with other study. In other study pitavastatin found that LDL-C and TC decreased by 40% and 31% in patients who received pitavastatin 2mg/d and by 48% and 37% in patients who received pitavastatin 4 mg/d on 16 week (Kajanami et al 2000). Previous study has reported that pitavastatin (2mg/d) showed percent reduction of LDL-C (11.6%) and TC (13.4%) from baseline on week 8 (Park et al 2005). In our study, pitavastatin 2mg/d decreased to LDL-C and TC by 151±7 (mg/dL) and 240±13 (mg/dL) respectively on week 12 from baseline. This suggests that significantly reduction in LDL-C and TC occurs over long term period. In other study pitavastatin (2mg/d) for 8 weeks showed percent decreased in LDL-C (42.8%), TC (35.4%) and Apo B (33.3%) (Kawashiri et al 2008). Our study reported improvement in HDL-C was 21% on week 52 from baseline. In another study on
308 patients with doses of 2, 4 and 6 mg for 44 weeks following an 8 week run-in on 2 mg od, mean LDL levels dropped from 5.22 to 3.13 mol/l by the end of 52 weeks. TG levels fell by 25-31% (baseline mean 2.9 mmol/l) and HDL cholesterol levels rose by 11% (baseline mean 1.45 mmol/l). Adverse events were minimal. 4.8% of the subjects had raised CPK levels (1.5-5×ULN), 2.9% had raised ALT and AST and only 2.6% were noted to have raised ALT levels (Kajinami et al 2000). The results reported in this study were in line with our study, there was no significant elevation on hepatic enzymes, hsCRP and CK-MB till 52 week. Thus the safety profile was found to be similar with the currently available statins. Our study suggests that pitavastatin is more effective than atorvastatin in reducing the LDL-C, Apo B and TC and improves the HDL-C on long term use. Pitavastatin effectively reduces these lipoprotein levels (LDL-C, TC and Apo B) levels during initial treatment period which is in line with other previous study. Our study suggests that long term use of pitavastatin for reductions in LDL-C is safe and effective. Yet, no study observed long the long term effect of pitavastatin on lipoprotein levels. Thus, study showed use of pitavastatin found to be effective and safe at minimal dose for reduction in low density lipoprotein cholesterol, total cholesterol and apolipoprotein levels and attainment of NCEP ATP III target goal for preventive management of ischemic heart disease patients.

In our second subset of study we studied the efficacy and safety of antithrombin agents (bivalirudin vs. heparin) as part of an early invasive strategy in IHD patients presenting with ACS and undergoing PCI with provisional use of GP IIb/IIIa inhibitor. Most ACS caused by intracoronary thrombus superimposed on disrupted atherosclerotic plaque and subsequent thrombosis leads to MI. Aspirin and heparin, the main cornerstones of therapy for ACS, reduces the risk of MI and death (Collaborative review of randomized trial 1994, Eikelboom et al 2000) However, patients with UA or AMI still remains at risk for recurrent ischemic events, suggesting that intracoronary thrombus formation is incompletely attenuated by aspirin and heparin (Weitz et al 2002). High concentrations of thrombin are generated by tissue factor exposed at sites of arterial injury (Chesebro et al 1991). When bound to fibrin (Hogg et al 1989, Weitz et al 1990), fibrin degradation products (Weitz et al 1998) or subendothelial matrix (Bar-Shavit et al
1998), thrombin is resistant to inactivation by the heparin/antithrombin complex. Bound thrombin remains enzymatically active, triggers thrombus growth by activating factor V, VIII, and XI (Kumar et al 1994), thereby amplifying thrombin generation. Bound thrombin also activates platelets (Kumar et al 1995), at least in part, via thromboxane A2-independent pathways that are not blocked by aspirin. The goal of most treatment regimens is to block thrombin generation or inhibit its activity. Direct thrombin inhibitors were developed to overcome the inability of the heparin/antithrombin complex to inactivate bound thrombin. Till date, clinical data supporting bivalirudin as an alternative to heparin during PCI was particularly noteworthy for evidence of substantial reduction in bleeding complications in conjunction with diminished ischemic events (Bittl et al 1995). The ATBAT trial (Mahaffey et al 2003) proved the safety and efficacy of bivalirudin in coagulation during PCI. The HERO-2 trial (White et al 1997) depicted that bivalirudin can replace heparin in management of MI. The CACHET trial (Lincoff et al 2002) as well as the REPLACE-1 trial (Lincoff et al 2004) illustrated that bivalirudin can significantly decrease the incidence of MI, revascularization and major hemorrhage as compared to heparin. The recent REPLACE-2 study (Bakhai et al 2006) showed that bivalirudin; in addition to provisional GP IIb/IIIa is not inferior to heparin plus GP IIb/IIIa and is associated with less bleeding. Our results depicted the safety of bivalirudin, with only two cases of death as compared to four deaths and two cases of rehospitalization in heparin treated group within 30 days of antithrombin agents. The protection from adverse events giving bivalirudin in the present study was notable. 6% provisional use of GP IIb/IIIa inhibitors comparable to 6% in the REPLACE-2 trial (Bakhai et al 2006) showing high efficacy of bivalirudin even in the absence of GP IIb/IIIa inhibitors.

In the ATBAT trial (Mahaffey et al 2003), TIMI grade III flow was seen in 94% of patients. In our study 95% of patients achieved TIMI III flow which is in line with the ATBAT trial. Incidences of bradycardia episodes 46 hours after PCI, surgical revascularization, no-reflow requiring a temporary intra-aortic balloon and HIT developed thrombocytopenia was observed in patients after receiving bivalirudin and GP IIb/IIIa inhibitors. In the CACHET trial (Lincoff et al 2002), combined incidences of MI, revascularization and major hemorrhage reported within 7 days was 3.55%.
Revascularization was seen in 2.1% of patients. Non Q-wave MI was detected following PCI in 2.1%. In the REPLACE-1 trial (Lincoff et al 2004) major bleeding occurred in 2.1% of patients. Blood transfusions were required in four patients. Thrombocytopenia was observed in 1.0% of patients. A quadruple efficacy and safety end-point of death, MI, repeat revascularization or major bleeding occurred in 7.1% of patients. In the REPLACE-2 trial (Lincoff et al 2004), rates of major bleeding were 3.9%. Thrombocytopenia <100,000/mm³ and <50,000/mm³ reported in patients was 0.7% and 0.3% respectively. Transfusion of RBC and platelets observed in patients was 1.3% and 0.3% respectively. In the ACUITY trial (Stone et al 2007), the composite incidences of death, MI, unplanned revascularization occurred in 9% of patients. Major bleeding reported was 4%. In our study, we observed no incidence of major bleeding; however 3.19% of patient showed minor bleeding in bivalirudin treated patients which was significantly lesser than earlier studies. One cardiac death was reported on day 7/hospital discharge while no incidences of myocardial infarction, revascularization, sub-acute thrombosis and instent restenosis were reported in patients treated with bivalirudin. On day 30 one incident of non cardiac death due to acute renal failure was reported in bivalirudin group. One year follow-up was event free survival. Thus, the overall events reported in our study were significantly lesser than previous studies. The requirement of GP IIb/IIIa inhibitors was significantly lesser in patients treated with bivalirudin (6%) as compared to heparin (22%) treated patients in our study. No significant difference in duration of procedure was observed between both antithrombin agents, however, time to remove sheath after PCI was significantly lesser in bivalirudin group compared to heparin groups. The optimal epicardial blood flow and myocardial blush grade was significantly higher in bivalirudin treated patients. Thus, study demonstrated the use of bivalirudin is efficacious and safe in moderate to high risk IHD patients presenting with ACS and undergoing PCI, leading to reduction in ischemic cardiac complications and risk of bleeding. Bivalirudin can replace heparin, it can combat the limitations and outcome of gold standard antithrombin agent. It is cost effective and can improve the quality of life of patients.
In the third subset of our study, we showed the efficacy and safety of standard therapy followed by abciximab (GP IIb/IIIa inhibitor) vs. standard therapy alone in moderate to high risk IHD patients presenting with ACS and undergoing PCI. Aspirin, thienopyridines, and antithrombotics are mainstays of medical therapy (Gluckman et al 2005). PCI is an established therapeutic approach in moderate to high risk patients presenting with ACS (Mehta et al 2005). However, it still requires effective antiplatelet therapies in such patients and undergoing PCI. Because there is enhanced platelet activation and aggregation in ACS compared with stable coronary disease (Schulman et al 2004, Ault et al 1999, Gurbel et al 2004), more antiplatelet therapies may be more effective (Bhatt et al 2000). In meta-analysis of trials involving patients with ACS who were primarily medically managed, GP IIb/IIIa inhibitors resulted in reduced rates of death and MI and also showed positive effect in patients undergoing PCI during index hospitalization (Kastrati et al 2006). The effect of abciximab in decreasing ischemic complications in high risk patients undergoing percutaneous coronary revascularization has been proven in many clinical trials, such as the EPIC trial (EPIC Investigators, 1994), EPILOG trial (The EPILOG Investigators 1997, Clinical Study Report 2006). But it was accompanied by increase in the incidence of major bleeding complications.

The EPISTENT trial reported that the addition of abciximab led to a >50% reduction in death, MI and urgent revascularization (The EPISTENT investigators 1998) during PCI. The EPIC trial, in ACS patients with PCI at high risk for abrupt vessel closure reported that addition of abciximab leads to the reduction in death, MI, urgent revascularization and mortality. EPILOG trial in ACS patients with PCI all subsets reported in less death and MI (The EPILOG investigators 1997) on addition of abciximab. 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 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). Our study reported no MACE (death, revascularization, and recurrence of MI) in patients treated with abciximab. After 30 days of abciximab infusion, event free survival was observed in patients treated with abciximab along with standard therapy while in previous study MACE was reported to be
5.2%-5.4% in patients treated with abciximab with standard or low-dose heparin from the EPILOG trial (The EPILOG investigators 1997). The observed rate of MACE in the group that received standard therapy alone was 1.67%. The previous trials reported mild thrombocytopenia (<100,000/ml) in 2.5-5.6% and severe thrombocytopenia (<50,000/ml) in 0.9-1.6% for abciximab and standard therapy treated patients (Fergusson et al 1998). In our study, one mild thrombocytopenia (1.67%) was reported in patient treated with abciximab and standard therapy.

In our study one minor bleeding (1.67%, at 4 hour), two minor gum bleeding and hematoma (3.33%, at 6 hour) was reported after the infusion of abciximab while one event each of hematuria (1.67%, 24 hour) and thrombocytopenia (1.67%, day 7) occurred in patient treated with standard therapy alone during hospital stay. None of the patients reported the occurrence of major bleeding and thrombocytopenia on day 30 when treated with abciximab along with standard therapy. No clinical significant change was observed in hemoglobin/hematocrit value in both the therapies till 30 day follow-up. UFH is partly responsible for the development of early thrombocytopenia in abciximab treated patients. Therefore, concerning the risk of thrombocytopenia with abciximab treatment, LMWH seems preferable to abciximab. Patients treated with abciximab in addition to standard therapy showed significant improvement in ECG changes within 30 day as compared to patients treated with standard therapy alone. Thus, our study suggests that abciximab in conjunction with standard therapy has a similar safety profile as that of standard therapy alone (aspirin, clopidogrel and heparin) and will be effective in improving ischemic outcome in moderate to high risk IHD patients presenting with ACS and undergoing PCI. The incidences of bleeding and thrombocytopenia were lower than observed in previous studies of abciximab in high risk cardiac patients.

In our fourth subset of study we showed the efficacy and safety of aspiration catheter (medical device) in addition to the conventional therapy in IHD patients presenting with AMI and undergoing PCI. Microembolization may be a relatively frequent event among patients with ACS or after PCI. In the setting of primary angioplasty for AMI, the incidence of distal embolization is rather high, though it is not always observed angiographically, it is characterized by impaired myocardial perfusion.
despite reopening of the epicardial coronary artery. NR phenomenon has been documented in $\geq 30\%$ of patients after thrombolysis or PCI for AMI (Eeckhout et al 2001, Tanaka et al 2002). Embolization of atherosclerotic and thrombotic material in the distal microvasculature represents the likely cause of many of the silent or unexpected MIs following coronary intervention (Califf et al 1998). Distal embolization was related to reduced myocardial reperfusion, more extensive myocardial damage, and a poor prognosis (Henriques et al 2002, Stone et al 2002). Mechanical device such as aspiration catheter (component of PercuSurge Guardwire®) is manually and easily operated device. In our study, thrombus was removed successfully without any complication using aspiration catheter (100% device success). Removal of thrombus burden from the coronary artery of the patient who were treated with aspiration catheter along with the conventional stenting, lead to the significant restoration of epicardial flow (100% vs. 72%, $p<0.001$) and myocardial perfusion (92% vs. 60%, $p<0.001$) at the end of the procedure as compared to the patients treated with conventional stenting alone. Requirement of pre dilatation (24% vs. 56%, $p<0.05$) and post dilatation (4% vs. 20%, $p<0.05$) was significantly lesser in patient underwent aspiration in addition to the conventional stenting. Thus, total procedural time was significantly reduced following primary aspiration (19.4±6.38 vs. 26.96±10.37, $p<0.05$). The incidences of slow flow/no-reflow, distal embolization and side branch closure were significantly lesser due to aspiration which reduces the usage of GP IIb/IIIa inhibitors (25% vs. 75%, $p<0.001$) and intracoronary vasodilators (16% vs. 44%, $p<0.001$). ST segment resolution in patients was significantly higher (88% vs. 65%, $p<0.001$) due to aspiration as compared to conventional stenting at 24 hour of the PCI. Primary aspiration followed by conventional stenting leads to a significant reduction in implantation of DES (48% vs. 24%, $p<0.001$). In patients, who underwent primary aspiration on day 7/hospital discharge, (MACE 12%) which includes one event each of cardiac death, non-cardiac death and sub-acute thrombosis were recorded. However, in patients who underwent only conventional stenting (MACE 16%) which includes three cardiac deaths and one urgent revascularization was recorded. One cardiac death (4%) was reported in conventional stenting on day 30. No adverse clinical event was reported at one year follow up in both the groups.
Our study, reported event free survival on day 30 after aspiration while in previous study (TAPAS) MACE reported was 6.8% (36 of 529 patients) (Svilaas et al 2008). At day 30, one death was reported in patient underwent only conventional stenting which was comparatively lesser than reported in TAPAS study 9.4% (50 of 531). In our study, 88% of patients showed ST segment resolution at 24 hour of aspiration which was comparatively higher than that observed in TAPAS study (56.6%) (Svilaas et al 2008) and other previous study (REMEDIA trial) (Remedia investigators) reported 58% patients showed ST resolution >70% after PCI. Incidence of no-reflow/slow flow (4%) and distal embolization (0%) was comparatively lesser than reported in previous study (no-reflow 8%, so-flow 15% and distal embolization 8%) (REMEDIA trial) (Remedia investigators). Achievement of final TIMI III flow (100%) and TMP 3 grade (92%) was comparatively higher than reported in previous study (96% of patients and 64% of patients respectively) (REMEDIA trial) (Remedia investigators). Aspiration along with conventional stenting showed significant improvement in myocardial and electrocardiographic variables of reperfusion and rates of deaths and MACE. Use of aspiration catheter during PCI is economic and cost effective in treatment of patients presenting with AMI within 24 hr of onset of symptoms. Thus, our study suggests that the use of primary aspiration before index procedure in IHD patients presenting with AMI if carried out by experienced operators is cost effective and improves the long term cardiac outcomes, shows significant achievement of ST segment resolution, reduction in distal embolization rates and thrombus burden with better and faster optimal restoration of epicardial and myocardial perfusion and thereby reduces the procedural time.
**Preventive Management in IHD**

Early preventive therapy with pitavastatin has effectively and safely reduced the risk of ischemia at minimal dose as compared to atorvastatin in patients by decreasing the burden of bad blood cholesterol levels (LDL-C, TC and Apo B) and inhibiting the process of atherosclerosis in hyperlipidemic patients so as to prevent the future events of CAD.

**Therapeutic Management in IHD patients presenting with ACS**

Therapeutic management with drugs and device showed:

Novel direct antithrombin agent; bivalirudin has effectively reduced the thrombus load by achieving ACT, improved the epicardial and myocardial blush; decreased incidence of no-reflow and slow-flow, death, MI, repeat revascularization, sub-acute thrombosis, instent restenosis, major bleeding and use of GP IIb/IIIa inhibitors as compared to gold standard indirect antithrombin agent, heparin in the treatment of moderate to high risk IHD patients presenting with ACS and undergoing PCI as part of an early invasive strategy.

Addition of novel antiplatelet GPIIb/IIIa inhibitor; abciximab on top of the standard therapy (aspirin, clopidogrel and heparin) has effectively reduced the ischemic complications such as incidence of cardiac death, MI, urgent revascularization, sub-acute thrombosis/occlusion, bleeding and thrombocytopenia and improved ECG variables as compared to standard therapy in the treatment of moderate to high risk IHD patients presenting with ACS and undergoing PCI.

Primary aspiration during intervention procedure has effectively removed the distal emboli/thrombus burden in patients and thereby, decreased the incidence of distal embolization and side branch closure; there by achieved faster optimal restoration of epicardial and myocardial perfusion; reduced procedural time, usage of intracoronary vasodilators and GPIIb/IIIa inhibitors and improved ST segment resolution better than PCI without aspiration in IHD patients presenting with AMI and undergoing PCI.