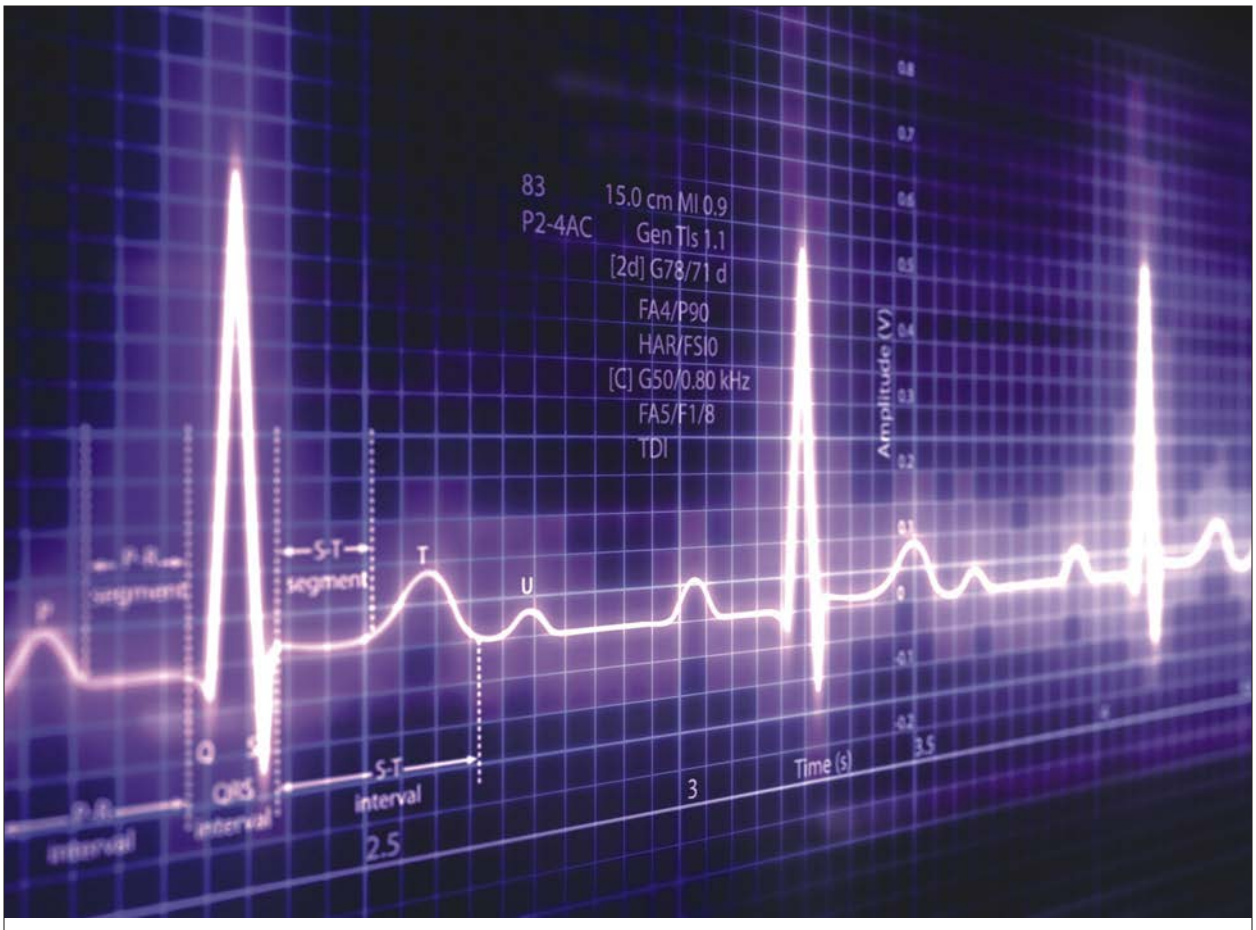

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Why Low Molecular Weight Heparin could not Gain the Confidence of Interventionists? An Overview

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Abstract: Presently coronary artery disease is considered as one of the major causes of mortality. The development of interventional cardiovascular technique such as coronary stunting has revolutionized the practice of interventional cardiology by overcoming partly some of the limitations of coronary angioplasty. During this procedure it produces vessel injury and induces thrombin generation and platelet activation with intertwined pathways, therefore Percutaneous Coronary Intervention (PCI) without anticoagulation appears unrealistic. It is almost universally accomplished with unfractionated heparin but the narrow risk-benefit ratio has led to search for better alternatives. The superiority of Low Molecular Weight Heparin (LMWH) over Un-Fractionated Heparin (UFH) is clear for ACS. Generally, the registries have reported a trend towards increased bleeding complications with LMWH than with UFH during PCI. In spite of its limitations, UFH proved to be the standard heparin therapy during PCI. This review study highlighted that LMWH requires further studies to determine their peri-catheterization monitoring, efficacy and safety profile.

Key words: LMWH (Low molecular weight heparine), PCI (percutaneous coronary intervention), UHF (unfractionated heparine), ACT (activated clotting time)

INTRODUCTION

Coronary artery disease is commonly due to obstruction of the coronary arteries by atheromatus plaque (Masri, 1995). Despite steady progress in the treatment of cardiovascular disease, it still remains as one of the major causes of mortality (Fuster, 1999). By the year 2020, coronary heart disease and stroke will hold first and fourth places respectively, in the World Health Organization's list of leading causes of disability (Murray and Lopez, 1997).

The main objective of therapy in patients with coronary artery disease is to alleviate symptoms of angina and reduce the risk of death or non-fatal myocardial infarction. Although, coronary angioplasty immediately reduces anginal symptoms in almost all the patients but its use is associated with death or nonfatal myocardial infarction in about 5% of patients and with restenosis requiring repeated angioplasty or bypass surgery in about 30% cases. The coronary stunting has revolutionized the practice of interventional cardiology by overcoming partially some of the limitations of coronary angioplasty, such as abrupt vessel closure due to coronary spasm, dissection or trauma, negative remodeling and to some extent restenosis (Bittl, 1996).

One of the major complications of coronary stenting is acute or sub-acute thrombotic occlusion within 24 h or within 2-14 days, respectively which occur in about four percent of patients after stent implantation and always results in myocardial infarction or death. Hence sub-acute thrombotic occlusion after stent implantation is the most serious problem (Wolfe *et al*., 1995) and carries a high incidence of unfavorable clinical outcome, including mortality and acute myocardial infarction (Topol, 1994).

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Coronary stenting results in significant platelet activation and enhanced surface exposure of adhesion receptors on activated platelets and plays a key role in the development of sub-acute vessel closure after coronary intervention (Gawaz *et al*., 1996). Platelet activation follows adhesion and can be initiated by several mechanical and chemical stimuli. Adhesion of platelets to collagen and other components of the sub-endothelial matrix and the presence of thrombin are among the strongest stimulators of platelet activation. The activation of platelets is associated with stimulation of several metabolic pathways, changes in the shape of platelets, activation of the glycoprotein IIb/IIIa receptor and induction of platelet coagulant activity (Landau *et al*., 1994). Both cellular (platelets) and serologic (thrombin) factors play a central role in thrombotic process (Lefkovits *et al*., 1995). Percutaneous coronary intervention involves the peri-procedural use of antiplatelet agents and anticoagulants, where as the use of platelet inhibitors are relatively well established but it has been suggested that Aspirin may prevent ischemia reactivation following heparin discontinuation (Theroux *et al*., 1992). However, subsequent studies showed that reactivation can occur among patients receiving Aspirin (Thrombin Inhibition in Myocardial Ischemia (TRIM) study group, 1996).

Coller and his colleagues were the first to demonstrate that a murine monoclonal antibody directed against the glycoprotein IIb/IIIa receptor, inhibited the binding of fibrinogen to platelets and thus inhibited platelet aggregation (Coller *et al*., 1983).

Anticoagulation during Percutaneous Coronary Intervention (PCI) is almost universally accomplished with unfractionated heparin since the advent of Percutaneous Coronary Intervention (PCI), intravenous unfractionated heparin has been the primary anti-thrombotic therapy to prevent periprocedural ischemic complications(Arjomand *et al*., 2002). The ACCP and the ACC/AHA/SCAI guidelines recommended that UFH should be administered to patients undergoing PCI (Smith *et al*., 1996) at a dose sufficient to produce an ACT of 250-350 sec, in patients receiving a GP IIb/IIIa inhibitor, a bolus dose of 50-70 IU kg^{-1} of UFH to achieve an ACT of greater than 200 sec. Also, recommend weight-based dose of 60-100 IU kg^{-1} and discourage routine post-procedural UFH infusion after uncomplicated PCI.

Un-Fractionated Heparin (UFH) is a glycosaminoglycan, composed of heterogeneous mixture of molecules of different weights; the anti-coagulation action of heparin is due to the binding of one-third of these molecules to anti-thrombin III, leading to a conformational change that markedly increases its ability to inactivate thrombin. The anticoagulant response to heparin varies greatly among patients. This may be due to different concentrations of heparin binding proteins and receptors on endothelial cells, which have to be saturated before a therapeutic plasma level can be achieved. Furthermore, natural inhibitors of heparin released from thrombus may decrease bioavailability of heparin (Hirsh *et al*., 2004). Moreover, thrombin is a potent direct activator of platelets and may consume antithrombin III which decreases availability for heparin to bind. Indeed a significant reduction in antithrombin activity may persist for 20 h or more, which is a vulnerable time for thrombus formation after unfractionated heparin for Percutaneous Coronary Intervention (PCI) reported by William *et al*. (1999). Increased level of both prothrombin fragment (free thrombin generation) and fibrinopeptide A thrombin activity have been observed after discontinuation of unfractionated heparin administered during Percutaneous CoronaryIintervention (PCI) which may play role in rebound thrombosis after discontinuation (Smith *et al*., 1996).

It was also observed that un-fractionated heparin directly activates platelet and enhances the response of platelets to low level of agonist Adenosine Diphosphate (Xiao and Theroux, 1998). This prothrombotic aspect of unfractionated heparin may have clinical consequences. For example, 33% of myocardial infarctions were observed following discontinuation of unfractionated heparin in GUSTO 1 trial within 10 h of unfractionated heparin discontinuation (Granger *et al*., 1996).

The clinical data in support of unfractionated heparin administration to patients with unstable angina is limited. In a meta-analysis of 1,353 patients from six trials, a marginal reduction in the

composite occurrence of death or myocardial infarction was observed over 2-7 days of unfractionated heparin therapy (Oler *et al*., 1996). The effect and dose of unfractionated heparin is being monitored during PCI by repeatedly performing Activated Clotting Time (ACT). The relationship of ACT to abrupt coronary closure is inverse and continuous (Nairns *et al*., 1996). While, the relationship to bleeding risk is direct and continuous (Hillegass *et al*., 1994).

Much of data in support of unfractionated heparin administration during PCI are nonrandomized and retrospective such as those reported by Ferguson *et al*. (1994), who noted that 80% of PCI procedures without complications had a procedural ACT of <300 sec. Eighty-five percent of those with complications had a procedural ACT of <250 sec. Hence, the optimal cut off for ACT during PCI was 300 sec. This retrospective study used Hemochron technology to measure the ACT (Ferguson *et al*., 1995).

Interestingly, when the same blood sample is tested by other available technology for measuring ACT with Hemotec, the resultant ACT was 30% lower than that observed with Hemochron. Thus, it is diffult to determine an optimal of ACT for a given technology during PCI (Ferguson *et al*., 1994).

Despite the widespread use of unfractionated heparin, the narrow risk-benefit ratio, has led to search for better alternatives. One such treatment has emerged through the depoymerization of unfractionated heparin to low molecular weight fragments (Hirsh *et al*., 1995).

Low molecular weight heparin binds less avidly to plasma and tissue proteins then unfractionated heparin, has higher bioavailability and exerts more durable and predictable therapeutic effects. It has more pronounced effect on Factor Xa than on thrombin, so that its antithrombotic effect is not reflected by the activated partial thromboplastin time. Because of resistance to platelet factor 4, LMWH is more successful in attenuating thrombin generation even in the presence of activated platelets (Samama *et al*., 1994).

Low Molecular Weight Haparin (LMWH) in particular enoxaparin, has already been established as first line of choice for unstable angina and Non-ST-Elevation Myocardial Infarction (NSTEMI) stated by Braunwald *et al*. (2002). Increasing evidence suggested that LMWH may supersede unfractionated heparin in PCI and potentially replace it as the antithrombotic agent of choice across the whole spectrum of Acute Coronary Syndrome (ACS) reported by Wong *et al*. (2003). The use of LMWH before cardiac catheterization has been associated with favourable clinical outcomes in patients with UA/NSTEMI. Retrospective analysis of the ESSENCE and TIMI-IIB trials suggested that the superior therapeutic effect of enoxaparin relative to unfractionated heparin is even more pronounced in patients who proceed to cardiac catheterization than those who are managed medically (Fox *et al*., 2000). As far as safety of LMWH enoxaparin is concerned, in both ESSENCE and TIMI-IIB trials the patients receiving enoxaparin who underwent subsequent revascularization had rates of major bleeding similar to those seen in patients receiving unfractionated heparin. In these trials LMWH therapy was discontinued before catheterization and interventional procedures were performed using unfractionated heparin. More recent observational data suggests that once LMWH therapy has been initiated, it may be continued safely as a procedural anticoagulant, without switing to unfractionated heparin (Guzman *et al*., 1999).

Collet *et al*. (2001) evaluated the strategy of transition to PCI in 451 patients receiving standard enoxaparin therapy for UA/NSTEMI (1 mg kg^{-1} twice daily SC). Out of this, 132 patients underwent PCI with no additional bolus during the procedure. Twenty five percent of these patients also received a GP IIb/IIIa inhibitors. There was no in-hospital abrupt coronary closure or urgent revacularization in any of the PCI patient, the incidence of death/mi at 30 days was 6.2% in the population as a whole and 3% in the PCI cohort. These observations are comparable favorably with those of previous studies. For example, in Abciximab plus low dose unfractionated heparin arm of EPILOG trial 1997 in which the lowest rates of both the major bleeding and ischemic events were observed. The incidence of death/mi at 30 days was 3.8%, the incidence of in-hospital major bleeding was 3.1%. The experience

of Collet *et al*. (2001) suggested that patients treated with standard dose of enoxaparin subcutaneous in UA/NSTEMI may safely undergo PCI within 8 h of the last subcutaneous injection without additional anticoagulant (EPILOG Investigators, 1997).

Evidence exists that intravenous LMWH can be used as a procedural anticoagulant during cardiac catheterization with and without concurrent uses of GP IIb/IIIa inhibitors. Several recent observational studies and trials were performed using LMWH enoxaparin for patients undergoing PCI procedures, including the National Investigators Collaborating on Enoxaparin 2001 registry studies (NICE 1 and 4). In NICE 1, enoxaparin 1 mg kg^{-1} was given at the time of PCI without concurrent GP IIb/IIIa inhibitor. At 30 days major bleeding events occurred in 1.1% of patients, minor bleeding in 6.2%, death/mi or revascularization in 7.7%. In NICE 4 study a total of 818 patients received enoxaparin by standard dose 0.75 mg kg^{-1} intravenous with Abciximab bolus and 12 h infusion 0.125 ug/kg/min to maximum of 10 ug/kg/min. At 30 days major bleeding occurred in o.4%, minor bleeding in 6.6%, death/MI or urgent revascularization in 6.8% (Kereiakes *et al*., 2001).

Choussat *et al*. (2002) evaluated a lower dose of intravenous enoxaparin, 0.5 mg kg^{-1} bolus, in 242 patients undergoing elective PCI with clinical and safety outcomes comparable to those seen in other registries.

Superior yield of the new strategy of enoxaparin, revascularization and glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial showed that synergy is the largest trial to investigate LMWH in the catheterization setting and compared enoxaparin (1 mg kg^{-1} subcutaneously every 12 h) with UFH (60 IU kg^{-1} IV bolus followed by 12 IU/kg/h) in 10,027 high-risk ACS patients intended to receive primary PCI. The end point of death (3.2 with enoxaparin vs. 3.1 with UFH) or MI (11.7 with enoxaparin vs. 12.7 with UFH) at 30 days resulted in no significant differences. Of note, Thrombolysis in Myocardial Infarction (TIMI) major bleeding rates (9.1% with enoxaparin vs. 7.6% with UFH, $p = 0.008$) and Coronary Artery Bypass Graft (CABG)-related hemorrhage rates (6.8% with enoxaparin vs. 5.9% with UFH, $p = 0.08$) were higher in patients randomized to receive enoxaparin. Investigators concluded that enoxaparin was a safe and effective alternative to UFH and that the benefits of the agent should be balanced with the modest increase in bleeding risk (Ferguson *et al*., 2004).

Similarly, the recently completed STEEPLE trial in late 2005 compared the safety of enoxaparin with that of UFH in non emergent PCI. The patients receiving enoxaparin 0.5 mg kg^{-1} and enoxaparin 0.75 mg kg^{-1} had significantly lower rates of major bleeding compared with UFH (0.9% vs 2.6%, $p = 0.004$ and 1.2% vs 2.6%, $p= 0.015$, respectively) and investigators concluded that enoxaparin is a safe and effective alternative to UFH in elective PCI (Steeple, 2005).

The ExTRACT-TIMI 25 trial, of which the results were announced at the 2006 ACC Scientific Session, compared the safety and efficacy of enoxaparin to UFH in STEMI patients with or without PCI and found enoxaparin superior to UFH for 48 h, but with an increase in major bleeding. The primary efficacy end point of death or non-fatal recurrent MI through 30 days of randomization occurred in 12% of patients treated with UFH and in 9% of patients treated with enoxaparin. This resulted in a 17% relative risk reduction in patients treated with enoxaparin ($p<0.001$). The primary safety end point of major, minor and minimal bleeding resulted in higher rates of major bleeding in patients treated with enoxaparin c compared to UFH (2.1% vs 1.4%[$p<0.001$]), respectively (Antman *et al*., 2006).

In order to minimize thromboembolic events, the use of effective and safe anticoagulation therapy is needed during PCI although the optimal dose of Unfractionated Heparin (UFH), the most commonly used anticoagulant during PCI, remains unknown (Kokolis *et al*., 2004) but at the start of PCI, a 50-100 UI kg^{-1} bolus of UFH is now recommended. If GP IIb-IIIa inhibitors are given, the use of low doses of UFH (50-70 UI kg^{-1}) limits the bleeding complications (EPILOG Investigators, 1997). Also, weight-adjusted low doses appear at least as safe as fixed high doses (Boccara *et al*., 1997). Despite

the fact that UFH is considered the gold standard of antithrombin therapy in PCI there are some disadvantages. The potential advantages of LMWH over UFH include its greater affinity for Factor Xa, a reduced likelihood of protein and cellular binding (i.e., a more predictable dose response), relative absence of thrombin rebound, lack of sensitivity to PF4 and a lower incidence of thrombocytopenia (Choo and Kereiakes, 2001). The superiority of LMWH over UFH is clear for ACS. But there is a trend towards increased bleeding complications during PCI with LMWH than with UFH (Choussat *et al*., 2002; Ferguson *et al*., 2004; Steeple, 2005; Antman *et al*., 2006). LMWH being novel agent need more time to be tested in the cath laboratories and require more studies to determine their peri-catheterization (or it should be pre-catheterization) monitoring, efficacy and safety profile. However in my view point, this modality of anticoagulation will gain the confidence of interventional cardiologists being more effective and simple in the years to come.

REFERENCES

Antman, E.M., D.A. Morrow and C.H. McCabe, 2006. The Extract-TIMI 25 trial, Enoxaparin versus unfractionated heparin with fibronolysis for ST-elevation myocardial infarction. N. Engl. J. Med., 354: 1477-1488.

Arjomand, H., S.K. Surabhi and M. Cohen, 2002. Unfractionated versus fractionated heparin for percutaneous coronary intervention. Curr. Cardiol. Rep., 4: 327-333.

Bittl, J.A., 1996. Advances in coronary angioplasty. N. Engl. J. Med., 335: 1290-1302.

Boccara, A., H. Benamer and J.M. Juliard, 1997. A randomised trial of fixed high dose vs a weight-adjusted low dose of intravenous heparin during coronary angioplasty. Eur. Heart J., 18: 631-635.

Braunwald, E., E.M. Antman, J.W. Beasley, R.M. Califf and M.D. Cheitlin *et al*., 2002. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction 2002: Summary article: A report of the American college of cardiology/American heart association task force on practice guidelines (Committee on the management of patients with unstable Angina). Circulation, 106: 1893-1900.

Choo, J.K. and D. J. Kereiakes, 2001. Low molecular weight heparin therapy for percutaneous coronary intervention: A practice in evolution. J. Thrombolysis, 11: 235-246.

Choussat, R., G. Montalescot, J.P. Collet, E. Vicaut, A. Ankri and V. Gallois, 2002. A unique, low dose of intravenous enoxaparin in elective percutaneous coronary intervention. J. Am. Coll. Cardiol., 40: 1943-1950.

Coller, B.S., E.I. Peerschke, L.E. Scudder and C.A. Sullivan, 1983. A murine monoclonal antibody that completely blocks the binding of fibrinogen to platelets produces a thrombasthenic-like state in normal platelets and binds to glycoproteins IIb and/or IIIa. J. Clin. Invest., 72: 325-338.

Collet, J.P., G. Montalescot, L. Lison, R. Choussat, A. Ankri and G. Drobinski, 2001. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. Circulation, 103: 658-663.

EPILOG Investigators, 1997. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N. Engl. J. Med., 336: 1689-1696.

Ferguson, J.J., K.G. Dougherty, C.M. Gaos, H.S. Bush, K.C. Marsh and D.R. Leachman, 1994. Relation between procedural activated clotting time and outcome after percutaneous transluminal coronary angioplasty. J. Am. Coll. Cardiol., 23: 1061-1065.

Ferguson, J.J., P. Dohmen, J.M. Wilson, W.K. Vaughn and R. Khoshnevis *et al*., 1995. Results of a national survey on anticoagulation for PTCA. J. Invasive Cardiol., 1: 136-141.

Ferguson, J.J., R.M. Califf, E.M. Antman, M., Cohen and C.L. Grines *et al*., 2004. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. J. Am. Med. Assoc., 292: 45-54.

Fox, K.A.A., E. Antman and M. Cohen, 2000. Are treatment effects of enoxaparin (low-molecular-weight heparin) more marked in those undergoing percuataneous intervention: Results of ESSENCE/TIMI 11B Investigators [abstract]. Eur. Heart J., 21: 599-599.

Fuster, V., 1999. Epidemic of cardiovascular disease and stroke: The three main challenges. Circulation, 99: 1132-1137.

Gawaz, M., F.J. Neumann, I. Ott, A. May and A. Schomig, 1996. Platelet activation and coronary stent implantation: Effect of antithrombotic therapy. Circulation, 94: 279-285.

Granger, C.B., J. Hirsh, M. Robert, J.C. Califf and H.D. White *et al*., 1996. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: Results from the GUSTO-I trial. Circulation, 93: 870-878.

Guzman, L.A., R. Henquin and E. Gurfinkel, 1999. Role of enoxaparin in patients undergoing percutaneous revascularization in the setting of unstable angina: A TIMI 11B substudy [abstract]. Eur. Heart J., 20: 260-260.

Hillegass, W.B., C.R. Narins and B.C. Brott, 1994. Activated clotting time predicts bleeding complications from angioplasty. J. Am. Coll. Cardiol., 23: 184A-184A.

Hirsh, J., R. Raschke, T.E. Warkentin, J.E. Dalen, D. Deykin and L. Poller, 1995. Heparin: Mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy and safety. Chest, 108: 258S-275S.

Hirsh, G., G.W. Albers and H.J. Schunemann, 2004. The seventh ACCP conference on antithrombotic and thrombolytic therapy: Evidence-based guidelines. Chest, 126: 172S-173S.

Kereiakes, D.J., C. Grines, E. Fry, P. Esente and D. Hoppenstead *et al*., 2001. Enoxaparin and abciximab adjunctive pharmacotherapy during percutaneous coronary intervention. J. Invasive Cardiol., 13: 272-278.

Kokolis, S., E. Cavusoglu, L.T. Clark and J.D. Marmur, 2004. Anticoagulation strategies for patients undergoing percutaneous coronary intervention: Unfractionated heparin, low-molecular-weight heparins and direct thrombin inhibitors. Progress Cardiovascular Dis., 46: 506-523.

Landau, C., R.A. Lange and L.D. Hillis, 1994. Percutaneous transluminal coronary angioplasty. N. Engl. J. Med., 330: 981-993.

Lefkovits, J., E.F. Plow and E.J. Topol, 1995. Platelet glycoprotein IIb/IIIa receptot in cardiovascular medicine. N. Engl. J. Med., 332: 1553-1559.

Masri, A.., 1995. Ischemic Heart Disease, a Rational Basis for Clinical Practice and Clinical Research. Churchill Livingstone, New York, USA.

Murray, C.J.L. and A.D. Lopez, 1997. Mortality by cause for eight regions of the world: Global burden of disease. Lancet, 349: 1269-1276.

Nairns, C.R., W.B.J. Hillegass, C.L. Nelson J.E. Tcheng and R.A. Harrington *et al*., 1996. Relation between activated clotting time during angioplasty and abrupt closure. Circulation, 93: 667-671.

Oler, A., M.A. Whooley, J. Oler and D. Grade, 1996. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina: A meta-analysis. J. Am. Med. Assoc., 276: 811-815.

Samama, M.M., L. Bara and G.T. Gerotziafas, 1994. Mechanisms for the antithrombolic activity in man of low molecular weight heparins (LMWHs). Haemostasis, 24: 105-107.

Smith, A.J., R.E. Holt, J.B. Fitzpatrick, I.F. Palacios and H.K. Gold *et al*., 1996. Transient thrombotic state after abrupt discontinuation of heparin in percutaneous coronary angioplasty. Heart J., 13: 434-439.

Steeple, M.G., 2005. Safety and efficacy of enoxaparin in percutaneous coronary intervention patients. Proceedings of the European Society of Cardiology Annual Congress, 2005.

Theroux, P., D. Waters, J. Lam, M. Juneau and J. McCan, 1992. Reactivation of unstable angina after the discontinuation of heparin. N. Engl. J. Med., 327: 141-145.

Thrombin Inhibition in Myocardial Ischemia (TRIM) Study Group, 1996. A low molecular weight, selective thrombin inhibitor, inogatran vs. Heparin, in unstable coronary artery disease in 1209 patients. Eur. Heart J., 18: 1416-1425.

Topol, E.J., 1994. Caveats about elective coronary stenting. N. Engl. J. Med., 331: 539-541.

William, Jr. H.M., P.B. Kurnik, C.G. William, J.U. William J. and J.E. Siegel, 1999. Antithrombin activity during the period of percutaneous coronary revascularization relation to heparin use, thrombotic complications and restenosis. J. Am. Coll. Cardiol., 33: 1248-1256.

Wolfe, M.W., G.S. Roubin, M. Schweiger, J.M. Isner and J.J. Ferguson *et al*., 1995. Length of hospital stay and complications after percutaneous transluminal coronary angioplasty: Clinical and procedural predictors. Circulation, 92: 311-319.

Wong, G.C., R.P. Giugliano and E.M. Antman, 2003. Use of low-molecular-weight heparins in the management of acute coronary artery syndromes and percutaneous coronary intervention. J. Am. Med. Assoc., 289: 331-342.

Xiao, Z. and P. Théroux, 1998. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. Circulation, 97: 251-256.