INTRODUCTION

Peripheral arterial disease (PAD) is a growing health problem across the globe. It is a chronic and progressive disease affecting lower limb arteries most commonly due to atherosclerosis. Approximately 10 million individuals have PAD in the United States, with a prevalence that approaches ~ 10% in individuals aged >60 years[1]. Among the most severely affected, nearly 100,000 peripheral artery reconstructions will be performed annually. In India, the overall prevalence of PAD in the selected South Indian population was 3.2% and 6.3% in the diabetic population in year 2000[2]. Patients with PAD have coronary artery disease (CAD) and cerebrovascular disease (CVD) as comorbidities and have a mortality risk proportional to the severity of PAD[3].

Atherosclerosis is derived from the Greek words 'athero' meaning paste and 'sclerosis' which means hardening. It can be described as an arterial disease characterized by the formation of atheromatous plaques (composed of cholesterol and macrophages) and the narrowing of the artery (stenosis). Atherosclerosis develops mainly in elastic and muscular arteries that are medium or large in size[4]. Inflammation is a biological process that occurs in response to stimulus arising from substances (pathogens, damaged cells, toxins, irritants) that pose threats to the survival of cells and the organism as a whole. It involves the immune system (which produces white blood cells to destroy the harmful stimulus) and the vascular system (aids in leukocyte transport into cells). Atherosclerosis develops due to this factors including failure of the immune system to counteract or destroy modified low density lipoprotein (LDL), free radicals, infectious and or other harmful agents detected by the system as foreign or related diseased conditions[4,5]. The problem emanates from the inability of leukocytes (monocytes and T lymphocytes) to destroy or remove these foreign molecules resulting in the trigger of further immune response, which

causes the artery to become inflamed[4,6]. Inflamed cells produce free radicals, which participate in cell degradation.

The role of inflammation in PAD is becoming increasingly recognized. Biomarkers are molecules that serve as indicators of a biological state (e.g. biologic and pathogenic processes) in living systems[7]. Several inflammatory markers have been related to atherosclerosis, including C-reactive protein (CRP), Serum Fibrinogen (S. Fibrinogen) and lipoprotein(a) (Lp(a))[8].

CRP is an acute phase protein. It is primarily synthesized by hepatocytes, driven by interleukin-6 (IL-6) with synergistic enhancement of interleukin-1 (IL-1) or tumor necrosis factor (TNF)[9]. A rise in CRP levels by as much as 1000-fold is not uncommon in both infectious and noninfectious disorders, including myocardial infarction. Its predictive value can be estimated only through high-precision assays (high-sensitivity CRP [hsCRP]), with acceptable precision down to or below 0.3 mg/L (2.86 nmol/L)[9].

hsCRP has been associated with severity of PAD and with a higher risk of cardiovascular events and long-term mortality in these patients[10,11]. CRP elicits a multitude of effects on endothelial biology favoring a pro-inflammatory and pro-atherosclerotic phenotype. In vitro experiments reveal that CRP potently down regulates endothelial nitric oxide synthase (eNOS) transcription and destabilizes eNOS mRNA, resulting in decreased release of basal and stimulated nitric oxide (NO), a key endothelium-derived relaxing factor[12]. In a synchronous fashion, CRP has been shown to stimulate endothelin-1 and IL-6 release from endothelial cells[13]; up-regulate adhesion molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin[14]; and stimulates the release of monocyte chemotactic protein-1, a chemokine that facilitates leukocyte transmigration[15]. By

inhibiting NO production, CRP facilitates endothelial cell apoptosis and blocks angiogenesis[12]. Furthermore, CRP augments CD14 induced endothelial cell activation; potently up-regulates nuclear factor-κB (NFκB)[16], a key nuclear factor that facilitates the transcription of numerous pro-atherosclerotic genes; and inhibits bone marrow–derived endothelial progenitor cell (EPC) survival and differentiation[17]. EPCs have been suggested to play an important role in postnatal neovascularization, and the ability of CRP to inhibit progenitor cells may be an important mechanism inhibiting compensatory angiogenesis in chronic ischemia[18]. CRP also has direct pro-atherogenic effects in vascular smooth muscle cells (SMC)[19].

Recent evidence suggests that CRP directly up-regulates angiotensin type 1 receptor in vascular SMCs in vitro and in vivo and stimulates vascular smooth muscle migration, proliferation, neointimal formation, and reactive oxygen species (ROS) production[20]. However, it is also shown that CRP up-regulates complement-inhibitory proteins and protects endothelial cells from complement-mediated cell injury[21]. This suggests that a balance of pro-atherogenic and anti-atherogenic effects of CRP on the vessel wall may be important in the development of atherosclerosis[19].

Fibrinogen is a glycoprotein that circulates at high concentration in blood. Fibrinogen is the soluble precursor of fibrin. Elevated fibrinogen levels are associated with greater risk for cardiovascular events and with all-cause mortality in PAD subjects[22]. Epidemiological studies have demonstrated that elevated levels of circulating fibrinogen are associated with accelerated development of atheroma and coronary events in man[23]. Cell culture studies have shown that fibrinogen and its derivatives are chemotactic and mitogenic to (SMCs)[24,25].

Fibrinogen and its metabolites may lead to endothelial dysfunction through various mechanisms[26]. Several atherosclerotic lesions contain large amounts of fibrin, either in the form of wall thrombus in the intact surface of the plaque or scattered diffusely all over the plaque. This phenomenon is associated with a decrease in fibrinolytic activity and plasminogen concentrations[27]. It has been found that fibrin (intima) triggers cell proliferation, contributing to cell migration, and bonds fibronectin, which triggers cell migration and adhesion[28]. Fibrinogen and products of its decomposition mediate the transportation of adhesion molecules in the surface of endothelium and their further migration to the intima. The decomposition products located in the inner layer can trigger mitogenesis and synthesis of collagen, attract leukocytes, and enhance permeability as well as vascular tone. In advanced atherosclerotic plaques fibrin participates in the close linkage of LDL and lipid accumulation, leading to the creation of the lipid nucleus of atherosclerotic lesions[26].

It has a substantial effect on plasma viscosity and thus on vessel perfusion, particularly in small vessels such as capillaries. Elevated plasma viscosity provokes a marked reduction in capillary perfusion. Fibrinogen is often elevated in diabetics, and moreover, it has been shown that diabetic microangiopathy can be provoked by hemorheological anomalies[22].

Lipoprotein (a) is a heterogenous macromolecule first identified in 1963. During the 1980s elevated levels of Lp(a) were found to be associated with early myocardial infarction[29], CAD and stroke[30]. Recently, similar studies into the lipid profiles in patients with PAD have found evidence that Lp(a) is an independent risk factor for peripheral atherosclerosis[31].

Lp(a) is a heterogeneous macromolecule consisting of a LDL molecule that contains Apo B100 linked by a disulfide bridge to Apo A, which is a hydrophilic glycoprotein of the plasminogen family[32,33]. Lp(a) is less studied and its physiological role has not yet been entirely determined, but it is considered a cause of endothelial dysfunction[34].

Its activity appears to be facilitated by increased levels of homocysteine, LDL[35] and in diabetics. Apo (a) acts as a ligand that binds specifically to β2-integrin Mac-1; this enhances the recruitment of adhesion molecules and their migration into the endothelium[35]. It is through such interaction with Mac-1, Lp(a) induce the NFκB (a transcription factor that controls pro inflammatory genes) activation resulting in the synthesis of tissue factor (which is pro thrombotic) as well as other pro inflammatory molecules[34]. Lp(a) inhibits fibrin formation by preventing transforming growth factor β (TGF-β) activation[34]. The physiological role of TGF-β is to restrain inflammatory responses and hinder the migration and proliferation of SMC.

High plasma levels of Lp(a) are strongly associated with CAD, stroke, and PAD[32]. There is a positive correlation between high serum Lp(a) levels and restenosis after percutaneous coronary interventions[36,37], only Maca et al[38,39] have reported a similar strong relationship between Lp(a) and restenosis after peripheral percutaneous transluminal angioplasty (PTA) of the femoropopliteal segment.

Diabetes mellitus (DM) is one of the most important risk factors for developing PAD[1]. Moreover, the prevalence of this disease is rapidly increasing in the world. Furthermore, the duration of the disease worsens its vascular prognosis[40]. Raised glucose levels in the circulation may speed up the process of atherosclerosis through putative mechanisms such as oxidative stress and protein glycation of vessel walls[41].

Lipoproteins can undergo glycation in conditions of chronic hyperglycemia; the modified lipids form advanced glycosylation end product (AGE) which can be recognized by AGE receptors present on macrophages[6,42]. Oxidative stress in diabetics is due to the formation of ROS which promotes inflammation[6]. Glycated lipoproteins support the action of proinflammatory cytokines in the arterial endothelium[7]. Insulin resistance in patients with type 2 diabetes leads to hypertriglyceridaemia and dyslipidaemia (Figure 1), conditions that are characterized by low high density lipoprotein (HDL) levels with high VLDL (very low density lipoprotein) and LDL levels. In such patients, NO activity is impaired which implies that endothelium function is hindered. Colwell[43], noted that glyco-oxidation, production of free radicals, and reduced antioxidant defense systems are common in diabetics. These enhance lipoprotein oxidation and promote atherosclerosis.

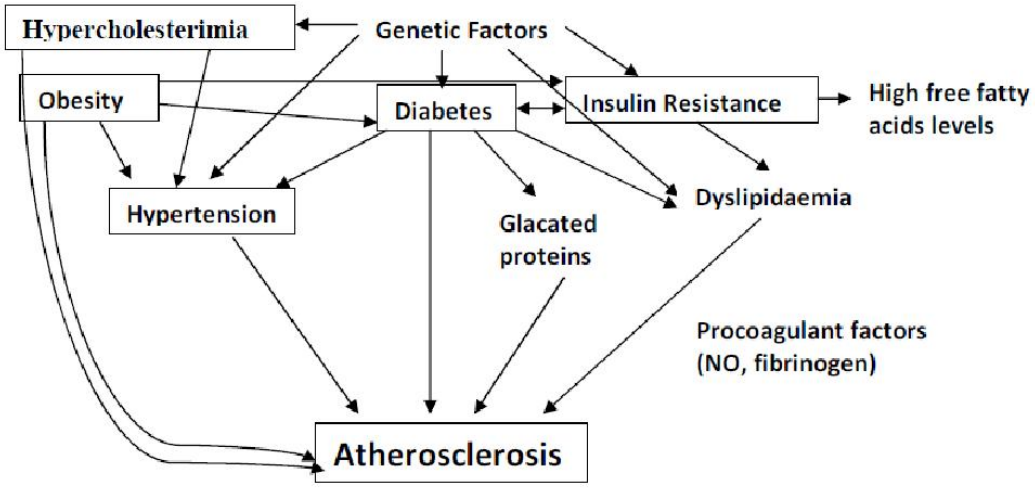


Figure 1 : Pathways and interactions of risk factors of atherosclerosis

Glycated hemoglobin (HbA1c) is formed by the slow irreversible, non-enzymatic glycation of valine and lysine residues in the haemoglobin molecule[44]. It is a useful test for characterizing dysglycemia as it is easier to perform than an oral glucose tolerance test and is independent of patient prandial status[45]. It reflects mean ambient fasting and postprandial glycaemia over a 2–3 months period. Elevated HbA1c levels (>7%) are associated with a higher incidence of microvascular and macrovascular complications in patients with type 1 and type 2 DM. In patients with diabetes, reducing plasma HbA1c levels by tight glycaemic control lowers the risk of subsequent microvascular disease. However, the relation of reduced HbA1c levels with macrovascular outcomes (e.g. stroke, ischemic heart disease, PAD) is less clear[46].

The outcomes of Endovascular therapy (EVT) in DM patients are not completely known. Controversial results about possible different results of EVT among diabetic and non-diabetic patients have been reported. EVT is currently accepted as the first step treatment in a most of patients that suffer from PAD. Continuous advances in this technique have allowed to increasingly offer therapeutic treatment of choice compared to the more aggressive intervention of open bypass. EVT obtains a high rate of successful primary outcome [47,48,49]. However, the need of reintervention after EVT should not be taken lightly, being close to 40% in the first 6 months after the procedure[50].

All three inflammatory markers are a risk factor for the development of atherosclerosis, and have a positive association with post angioplasty restenosis. The impact of DM on patency of EVT in PAD patients is probably less incidental than the previous inflammatory load in these patients.

Thus we outline our research to determine the effect of inflammatory burden both at pre operative and at 6 months in patients with PAD by measuring the levels of hsCRP, S. Fibrinogen, Lp(a) and studying their effect on patency after EVT.

AIMS AND OBJECTIVES

Primary objective:

- To determine the effect of pre-operative levels of hsCRP, S. Fibrinogen and Lipoprotein(a) on primary patency following Endovascular Therapy for infra inguinal peripheral arterial disease.

Secondary objective:

- To investigate if the presence of Diabetes Mellitus (HbA1c levels) affects these results.

REVIEW OF LITERATURE

Research has shown that inflammatory processes are involved in the onset and progression of PAD[51,52]. In particular, hsCRP a surrogate of systemic inflammation, is a powerful marker of this atherosclerotic manifestation[53,54,55]. Other circulating markers of inflammation in addition to hsCRP that are associated with cardiovascular disease and PAD are S. Fibrinogen and Lp(a)[53].

Fibrinogen levels are higher in subjects with PAD and are predictive of adverse cardiovascular events in this population[23]. To date, only few working groups have addressed the effect of different inflammatory markers on the development of restenosis in PAD patients after EVT.

Bleda S et al[56], conducted the prospective cohort study in patients with PAD. hsCRP and fibrinogen assessments were determined with 12-month follow-up period to determine the effect of inflammatory preoperative burden on the incidence of reintervention and mortality after EVT and to investigate if DM was involved in these results.

hsCRP and fibrinogen assessments were determined. 85 diabetic and 58 non-diabetic patients were included. Patients with clinical evidence of infection including cellulitis, osteomyelitis or deep space infection of the foot (Grade III, Category 6 Rutherford) were excluded. An increase between basal hsCRP (11.8mg/L (10.2; 21.5) versus 4.3mg/L (1.8; 13.9), $p < 0.001$) and fibrinogen levels (450mg/dL (425; 479.1) versus 369 mg/dL (268; 419), $p < 0.001$) and the incidence of death during follow up was found. A significant increase between higher hsCRP and fibrinogen basal levels and the incidence of reintervention during the follow-up period was also noted ($p = 0.001$ and $p = 0.04$, resp.,).There was no difference

between DM and non-DM patients in the 1-year need of reintervention (33.3% versus 45%, p = 0.15, resp.,).

Basal hsCRP and fibrinogen levels did not significantly differ between DM and non-DM patients who needed reintervention. They concluded that the prognosis of the EVT was likely marked by the previous inflammatory load, regardless of DM.

Belda S et al[57], conducted the study to determine the possible association between serum hsCRP and fibrinogen levels both pre intervention and during follow-up, and the outcomes of EVT and their association with the incidence of cardiovascular events or death in these patients.

It was a prospective cohort study in patients diagnosed with PAD in the iliac, femoral, popliteal, or distal sectors within Rutherford category 3-5 who underwent EVT de novo. They determined levels of hsCRP and fibrinogen before surgery and during the follow-up period (at 1, 3, 6 and 12 months), analyzed the possible association among inflammatory markers levels before EVT, during 1 year of follow-up and its variation during that year and the incidence of reintervention, reintervention-free survival, and the occurrence of cardiovascular events or death.

Over the course of 1 year, 246 patients underwent a revascularizing treatment of the lower limbs; 64 patients qualified for inclusion in this study. In these 64 patients, a significant increase between basal hsCRP and fibrinogen levels and the incidence of reintervention (p = 0.002 and p = 0.013, respectively) and death (p = 0.001 and p = 0.013, respectively) during follow-up was found. A significant increase between higher hsCRP basal levels and the incidence of cardiovascular events during the follow-up period was also noted (p = 0.004). Levels of basal hsCRP were related to reintervention-free survival after EVT (p = 0.04). On the basis of the rate of

hsCRP variation and its association with reintervention-free survival, they observed a progressive reduction of the levels of hsCRP until 12 months after the primary procedure.

They concluded that basal levels of inflammatory markers and their variation during follow-up allowed them to identify a subgroup of patients with PAD that will require a greater number of (and earlier) reinterventions after EVT and who will have higher rates of cardiovascular morbidity and mortality.

Bleda S et al[58], conducted a study to find out if CRP can predict the outcomes of lower extremity EVT in patients with PAD and to calculate a cutoff value that may be useful in identifying patients with a higher risk of EVT failure at 1 year.

It was a prospective, single-center study, with 121 patients(94 men; mean age 67.7±9.8 years) (excluding those with Rutherford Cat VI) undergoing EVT of lower limb lesions in an 18-month period were enrolled as a derivation set. In the subsequent 6 months, 53 patients (39 men; mean age 70.1±10.0 years) were enrolled as the validation set. Blood samples were collected before EVT and at 1 month postintervention from both sets of patients to measure CRP levels. The cohorts were followed for 1 year, and data on reinterventions were recorded. A cutoff CRP value was calculated with the highest sensitivity and specificity for EVT failure based on receiver operator characteristic (ROC) curve analysis. The cutoff value was confirmed in the validation set.

The area under the ROC curve relating preprocedure CRP levels to 1-year reintervention was 0.77±0.05. The highest likelihood ratio corresponded to a pre-EVT CRP value of 9.8 mg/L (likelihood ratio test=133, df=1, $p<0.001$). Reintervention before the first year after EVT was related to preprocedure CRP levels (HR 1.1, 95%

CI 1.05 to 1.2; p<0.001). These results were confirmed in the validation set (HR 1.1, 95% CI 1.02 to 1.18; p=0.008).

They concluded that CRP values can be used as an independent marker of EVT outcome. Baseline CRP levels >9.8 mg/L indicate increased risk of secondary interventions, which are often open surgical procedures.

Rudofsky G et al[59], evaluated any correlation of fibrinogen and hematocrit with the early success of balloon angioplasty for PAD and compare the outcomes of angioplasty in diabetic and non-diabetic patients.

From November 1997 to October 2000, 330 patients (246 men; mean age 63.6±10.9 years; 221 non-diabetic, 109 diabetic) with known PAD were treated with percutaneous procedures. The majority of patients (239, 72.4%) were Fontaine stage IIa or IIb; the remaining (91, 27.6%) had critical limb ischemia(CLI) (Fontaine stages III and IV). Fibrinogen and hematocrit assays were performed on all patients upon admission, and the results were then correlated with early angioplasty success.

With advancing PAD stage, fibrinogen concentrations increased significantly in both non-diabetic ($p < 0.006$) and diabetic ($p < 0.02$) patients, while angioplasty success rates declined by a factor of 3 in nondiabetics and 2 in diabetics. There was a significantly stronger association between low fibrinogen values and successful interventions relative to unsuccessful interventions ($p < 0.048$). Interestingly, compared with non-diabetics, the angioplasty success rate in diabetics was associated with significantly higher fibrinogen levels ($p < 0.044$) and lower hematocrit ($p < 0.022$).

Their findings appear to indicate that hemorheological factors, such as fibrinogen and hematocrit, can affect early angioplasty success. Moreover, high

fibrinogen concentrations appear to be detrimental to early angioplasty success. Interestingly, low hematocrit levels in diabetics may partially offset the negative effects of hyperfibrinogenemia.

Giovanetti F et al[60], conducted the prospective study to evaluate the influence of serum lipid sub fraction concentrations on arterial patency after PTA in patients with infra inguinal PAD.

From January 2007 to June 2008, a study was conducted involving 39 patients (29 men; mean age 68.66±10.0 years) with infra inguinal PAD in 41 limbs who had pre procedural lipid assessment and underwent successful PTA (<30% residual stenosis). Patient demographics, Fontaine clinical stage classification, Texas University Classification of ulcers, coexisting medical conditions, endovascular procedures, and lipid profiles were collected in a database. Follow-up included clinical and duplex ultrasound evaluation at discharge and at 1, 3, 6, and 12 months. To analyze any correlation between various lipid subfractions and the loss of primary patency (Cox proportional hazards modeling), the patients were dichotomized into high and low groups according to these thresholds: LDL-C >100 mg/dL, HDL-C <40 mg/dL, Lp(a) >30 mg/dL, and an Apo(B)/Apo(A)ratio >0.8 mg/dL.

Mean follow-up was 7.5 months (range 3–12). After 1, 3 and 6 months, the primary patency rates by Kaplan-Meier analysis were 94.9%, 73.7%, and 64.1% respectively. Restenosis at 6 months was significantly related to female gender (HR 95.9, 95% CI 6.8 to 1352.5, p = 0.001), HDL-C <40 mg/dL (HR 86.9, 95% CI 6.4 to 1183.1, p = 0.001), LDL-C>100 mg/dL (HR 9.6, 95% CI 1.6 to 57.4, p = 0.013), and Lp(a) >30 mg/dL (HR 6.1, 95% CI 1.4to 26.3, p = 0.016).

There results suggest that Lp(a), LDL-C, and HDL-C are independent risk factors for restenosis after infrainguinal PTA.

Gary T et al[61], evaluated the association between plasma lipoproteins and the development of superficial femoral artery (SFA) in-stent restenosis and reocclusion in patients with PAD.

Total 139 patients with SFA stenting and plasma lipoproteins measured after stent implantation were included. Stent restenosis was assessed with duplex scan after 3, 6 and 12 months. A stenosis grade was considered relevant if >50%.

Seventy-two patients experienced recurrence of their atherosclerotic disease, meaning restenosis of >50% within 1 year of follow-up. Ten of these patients had a stent occlusion. In the patients who experienced recurrence, the mean Apo B level was 105.8mg/dl versus 94.9 mg/dl in patients without recurrence ($p < 0.05$). Patients without recurrence had higher HDL cholesterol levels than patients with recurrence (39.7 vs. 34.7 mg/dl, $p < 0.05$). Comparing patients with a stent occlusion ($n = 10$) and those with a restenosis of 75–99% ($n = 28$), the patients with a stent occlusion had higher levels of plasma cholesterol (234.1 vs. 185.9 mg/dl, $p < 0.05$), apo B (135.3 vs. 99.8 mg/dl, $p < 0.05$), LDL cholesterol (160.3 vs. 113.6 mg/dl, $P < 0.05$), and low-density lipoprotein apo B (115.5 vs. 82.4 mg/dl, $p < 0.001$) than the patients with restenosis of 75–99% ($n = 28$).

They concluded that changes in the lipid profile could be one reason for the development of restenosis and for the development of reocclusion after SFA stenting.

Awad S et al[62], compared current revascularisation practice and outcome in diabetic and non-diabetic patients presenting with CLI to a single vascular surgeon. Data for 113 patients presenting with CLI were collected prospectively over a 3-year period. Forty-four (39%) were diabetic. Treatment was classified as percutaneous angioplasty, arterial reconstruction, primary major amputation, and conservative therapy. Main outcome measures were 30-day mortality, major amputation, survival and amputation-free survival.

No significant differences were found in the initial treatment options between diabetics and non-diabetics: angioplasty 39 vs 26%, surgical revascularisation 34% vs 33%, primary major amputation 9%vs 17%, and conservative treatment 11% vs 19% (p = Not significant in all). There were eight deaths (7%) within 30-days. At follow-up (1–44 months, median 14 months), rates of major amputation and death for the entire population were 23 and 8%, respectively. The 12-month cumulative survival and amputation-free survival rates were 90 and 72%, respectively. When comparing diabetic to non-diabetic patients, there were no significant differences in the 30-day mortality (6.8 vs 7.2%, p = 0.4), cumulative survival (93 vs 89% at 12 months, log-rank test: 0.00, p = 0.9), amputation-free survival (71 vs 73% at 12 months, log-rank test: 0.00, p = 0.99), and major amputation rates (22.7 vs 23.1% at 12 months, p = 0.96). Similarly, there were no differences in limb salvage rates between diabetic and non-diabetic patients undergoing revascularisation procedures (78 vs 90% at 12 months, log-rank test: 2.04, p = 0.15).

In current practice, an aggressive multidisciplinary approach in diabetic patients presenting with CLI leads to similar limb salvage, amputation-free survival, mortality, and major amputation rates to those seen in non-diabetic patients. The

presence of diabetes should not deter clinicians from attempting revascularisation by means of angioplasty or surgical reconstruction.

Bakken A et al[63], conducted the study regarding the implication of DM on long-term outcomes following EVT for SFA occlusive disease.

The study was conducted between 1986 and 2005, with three groups of patients were defined: non-diabetic patients, those with non-insulin-dependent DM (NIDDM), and those with insulin-dependent DM (IDDM). EVT (i.e., balloon angioplasty - adjuvant stenting in 38%) was initiated in 525 limbs in 437 patients (68% male; average age, 66 ± 14 years) for claudication failing conservative therapy or chronic CLI. Of these, 50% were non-diabetic, 26% had NIDDM, and 24% had IDDM. Analyses were separated by those presenting with claudication (61%) and those presenting with CLI (39%). Among patients presenting with claudication, those with IDDM had significantly lower assisted primary patency ($p < 0.01$) and a higher incidence of restenosis ($p = 0.04$). Patency at 3 years for non-diabetic, NIDDM, and IDDM were 62%, 72% and 54% (primary), and 81%, 86% and 65% (assisted primary), respectively. Patency and restenosis rates were associated with lesion calcification, TASC D lesion categorization, and acute peri procedural occlusion. Among patients presenting with CLI, patency and restenosis rates were equivalent across all groups; however, limb salvage was significantly worse for both groups of diabetic patients compared with non diabetic (NIDDM, $p = 0.01$; IDDM, $p = 0.02$). Reduction in limb salvage rates was associated with presence of tissue loss at presentation, end-stage renal disease and progression of distal disease on follow-up.

EVT for SFA occlusive disease yields lower assisted patency rates and higher restenosis rates for those patients presenting with claudication who have more advanced diabetes (i.e., IDDM). Among those patients presenting with CLI,

particularly those with tissue loss, limb salvage rates are lower for the diabetic groups (NIDDM and IDDM) despite equivalent patency and restenosis rates.

DeRubertis BG et al[64], aimed to assess differential outcomes in between diabetics and non-diabetics in lower extremity percutaneous interventions.

Retrospective study between 2002 and 2005 with 291 patients studied with respect to patient variables, complications, and outcomes for percutaneous interventions performed for PAD with a mean follow-up of 11.6 months (range 1 to 56 months).

A total of 385 interventions for PAD with claudication (52.2%), rest pain (16.4%), or tissue loss (31.4%) were analyzed, including 336 primary interventions and 49 reinterventions (mean patient age 73.9 years, 50.8% male). Comorbidities included DM (57.2%), chronic renal insufficiency (18.4%), hemodialysis (3.8%), hypertension (81.9%), hypercholesterolemia (57%), CAD (58%), tobacco use (63.2%). Diabetics were significantly more likely to be female (55.3% vs 40.8%), and suffer from chronic renal insufficiency (23.5% vs 12%), a history of myocardial infarction (36.5% vs 18%), and and less than three-vessel tibial outflow (83.5% vs 71.8%), compared with non-diabetics, although all other comorbidities and lesion characteristics were equivalent between these groups. Overall primary patency (±SE) at 6, 12 and 18 months was 85± 2%, 63± 3% and 56 ±4%, respectively. Patients with diabetes suffered reduced primary patency at 1 year compared with non-diabetics. For non-diabetics, primary patency was 88± 2%, 71 ±4%, and 58 ±4% at 6, 12 and 18 months, while for diabetics it was 82± 2%, 53± 4%, and 49± 4% respectively (p = 0.05). Overall secondary patency at 6, 12 and 18 months was 88± 2%, 76 ±3%, and 69± 3%, and did not vary by diabetes status. One-year limb salvage rate was 88.3% for patients with limb-threatening ischemia, which was also

similar between diabetics and non-diabetics. While univariate analysis revealed that female gender, less than three-vessel tibial outflow, and a history of tobacco use were all predictive of reduced primary patency ($p < 0.05$), none of these factors significantly impacted secondary patency or limb-salvage rate. Furthermore, only limb-threatening ischemia remained a significant predictor of outcome on multivariate analysis, suggesting that the poorer primary patency in diabetics is related primarily to their propensity to present with limb-threatening disease compared with non-diabetics.

Patients with diabetes demonstrate reduced primary patency rates after percutaneous treatment of lower extremity occlusive disease, most likely due to their advanced stage of disease at presentation. However, despite a higher reintervention rate, diabetics and others with risk factors predictive of reduced primary patency can attain equivalent short-term secondary patency and limb-salvage rates. Therefore, these patient characteristics should not be considered contraindications to EVT.

Dick F et al[65], assessed the efficacy of endovascular-first vs surgical-first revascularization stratified for the presence of diabetes. It was a prospective cohort study, with 1-year follow up, was conducted in a consecutive series of 383 patients (45.7% had diabetes) presenting 426 limbs with chronic CLI. Interventions were endovascular (PTA cohort, 207 limbs) or surgical (SURG cohort, 85 limbs) revascularization. Conservatively treated patients without revascularization (NON REVASC cohort, 108 limbs) were used as a reference. The main outcome measures were sustained clinical success, defined as survival without major amputation or repeated target extremity revascularization (TER), and a categoric upward shift in clinical symptoms according to the Rutherford classification.

Sustained clinical success of revascularization was significantly better in non-diabetic patients (HR, 0.48; 95% CI, 0.29 to 0.72; p = 0.001 [SURG cohort]; HR, 0.53; 95% CI, 0.35 to 0.78; p = 0.002 [PTA cohort]) compared with diabetic patients (HR, 0.78; 95% CI, 0.44 to 1.43, p = 0.45 [SURG cohort]; HR, 0.83; 95% CI, 0.55 to 1.27, p = 0.40 [PTA cohort]). Repeated TER significantly improved clinical success, which became equivalent between diabetic and non-diabetic patients (HR, 1.02; 95% CI, 0.7 to 1.4). In multivariate analysis, treatment success was not influenced by mode of initial revascularization, neither in diabetic nor in non-diabetic patients. Cumulative 1-year mortality was 30.4%, with a trend of increased mortality in patients with diabetes (HR, 1.45; 95% CI, 0.98 to 2.17; p = 0.064). Limb salvage rates were similar in treatment cohorts, also if stratified for diabetes (HR, 1.04; 95% CI, 0.62 to 1.75).

Diabetic patients with chronic CLI benefit from early revascularization. To achieve this benefit, multiple revascularization procedures may be required, and close surveillance is therefore mandatory. Choice of initial revascularization modality seems not to influence clinical success.

O'Connor D et al[66], conducted the study to determine if the level of HbA1c has any effect on disease severity in diabetic patients with limb threatening ischemia. A retrospective review of all patients presenting with limb threatening ischemia between January 1 and December 31, 2007 was conducted. All patients underwent conventional arteriography prior to intervention. Of 148 patients, 73 were diabetics with a HbA1c level performed within 3 months of presentation. Patients were placed into high (>7) and low (<7) HbA1c groups and data was collected on type of presentation, comorbidities, anatomic level of disease, tibial artery patency, need for

amputation, contralateral disease, need for an open versus an endovascular procedure, and freedom from intervention.

Thirty-six patients had HbA1c levels above 7.0 and 37 had levels below 7.0 (mean 7.64 ± 2.04, range 5.1–14.7). There were no statistically significant differences in the two groups in comorbities, average age, initial gangrene at presentation, aspirin or statin use, or smoking status. Patients in the high group were more likely to have had a previous attempt at revascularization (23 versus 11, p = 0.0049). There was no difference in the presence of contralateral disease (7 versus 4, p = 0.3447) or in the number of patent tibial vessels. Patients with low HbA1c levels were more likely to have the peroneal artery affected (17 versus 8, p = 0.048). In addition, TASC II classifications of iliac and femoral popliteal disease were similar between the two groups.

In conclusion glucose control measured by HbA1c does not appear to affect severity of disease or need for reintervention in diabetics with limb threatening ischemia. This suggests other factors related to diabetes may play a role in peripheral vascular disease. Larger, prospective studies are needed to assess the affect of glucose control in limb threatening ischemia.

To date, only few working groups have addressed the effect of different inflammatory markers on the development of restenosis in PAD patients after EVT. Controversial results about possible different results of EVT among diabetic and non-diabetic patients have been reported [67,68]. The goal of this study was to determine the effect of inflammatory preoperative burden on the incidence of reintervention after EVT for PAD patients, and to investigate the role of DM.

MATERIAL AND METHODS

All patients presenting to Jain Institute of Vascular Sciences (JIVAS) with chronic CLI categorized by Rutherford classification for chronic limb ischemia[69] with imaging pattern suitable for infra inguinal EVT revascularization during the period between April 2013 and March 2014 were prospectively evaluated.(30 patients)

This was a single centre, non-randomized, prospective study.

Inclusion Criteria:

- >18 years of age.
- All patients who underwent technically successful infra inguinal endovascular therapy for PAD (Rutherford Category IV, V, VI)[69] at JIVAS, Bhagwan Mahaveer Jain Hospital, Bangalore.
- Patient giving consent for participating in study.

Exclusion Criteria:

- Patients with autoimmune disease, on immunosuppressive treatment, acute myocardial infarction, stroke, any major surgery or severe trauma within 30 days prior to intervention.
- Patients with lesions proximal to Common Femoral Artery.
- Patients not achieving technical success.
- Patients undergoing hybrid procedures (open + endovascular) for infra inguinal lesions.

Once the patients were enrolled in the study, their demographics were recorded; they were assessed for medical risk factors like DM, Hypertension (HT), CAD and CVD as evident by history which was then corroborated with their previous laboratory reports and investigations at this admission. **DM was defined** by a baseline blood glucose of >126 mg/dL, HbA1C (>6.5%), or the need for glucose-

lowering treatment according to the World Health Organization criteria[70]. **HT was defined as** having high blood pressure (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg) and/or receiving antihypertensive treatment for at least 1 year before inclusion in the study[71]. **CAD was defined as** a history of angina pectoris, myocardial infarction, congestive heart disease, or prior coronary artery revascularizations[63]. **CVD was defined as** a history of stroke, transient ischemic attack, or carotid artery revascularization[63]. Other factors noted were presence of tobacco usage (smoking/chewing) and chronic kidney disease (serum creatinine >1.5 mg/dL)[72]**. Smoking habit was defined as** active smoker when the patient smoked at the time of the inclusion or gave up the habit in a period lower than 6 months[56].

A thorough history with general and local examination was carried out and careful noting of the pulse status of both lower limbs along with ankle brachial index (ABI) and pulse volume recording (PVR) was done. Wounds were categorized according to wound characteristic staging from WIFI classification (Wound characteristic, Ischemia, and Foot Infection)[73]. With respect to wound categorization, both the Fontaine and Rutherford classifications of lower extremity ischemia lack sufficient detail and other diabetic foot ulcer classifications such as perfusion, extent/size, depth/tissue loss, infection, sensation (PEDIS), University of Texas, variants of sepsis, arteriopathy, denervation (SAD) classification doesn't have a role in classifying non-diabetic patients with wound[73].

Along with routine blood investigations including liver and renal function tests, the inflammatory markers (hsCRP, S. Fibrinogen and Lp(a)) with HbA1C levels were recorded before any intervention for each patient enrolled in the study.

Blood sampling

Early morning sample was drawn by clean venipuncture from an antecubital vein using a 21-gauge x 3/4' needle (BD Vacutainer® Safety-LokTM Blood Collection Sets with Pre-Attached Holder); at admission and 6months of follow up. To avoid procedural deviations, all blood samples were taken by the same physician applying a light tourniquet, which was immediately released. 3cc of blood was drawn into a Red Cap Vacutainer (BD Vacutainer®) for hsCRP and Lp(a) each. For S. Fibrinogen the blood sample was anti coagulated with 3.8% trisodium citrate in proportions of 9:1, in blue cap Vacutainer (BD Vacutainer®). Another, 3cc of whole blood was collected in purple Cap Vacutainer (BD Vacutainer®) for HbA1c.

Measurement of hs-CRP, S.Fibrinogen, Lp(a) and HbA1c

For the measurement of hsCRP, sample was spun at 3000 rpm (Figure 2) for 20 minutes and then frozen at −70˚C until its analysis. Level was measured by ultrasensitive automated immunoassay (Roche Diagnostics), with detection in the lower limit of 0.2mg/L and a variation rate of 4.2% in 4mg/L and 6.3% in 1mg/L[56].

Figure 2 : Centrifugation machine

For S. Fibrinogen the blood sample was centrifuged at 3500 rpm for 7 minutes. If testing was not done within twelve hours of collection the plasma was stored at –70°. The test was done using electromechanical clot detection technique (Clauss method) by STA Compact Max®. (Diagnostic Range: 200-400mg/dl)

On the STA-Compact, the fibrinogen concentration in plasma was determined quantitatively by the Clauss clotting method. This test method involves measuring the rate of fibrinogen to fibrin conversion in diluted sample under the influence of excess thrombin. Since under these conditions the fibrinogen content was rate limiting, the clotting time can be used as a measure of the concentration of the fibrinogen and in fact the clotting time is inversely proportional to the level of fibrinogen in the plasma.

Clot detection by the STA-Compact involves an electromagnetic-mechanical system. The oscillation of a steel ball within the cuvette with the thrombin and diluted plasma was monitored by the STA-Compact. When the oscillation of the steel ball was stopped by clot formation, the sensor registers the time in seconds. The time was translated into fibrinogen concentration from a fibrinogen standard curve, stored on the STA Compact.

Lp(a) was determined using antiserum antibody reactions using immunoturbidometric assay (Incstar corporation, Stillwater, MN, U.S.A.). (Normal Range: <30mg/dl)[74].

HbA1c was determined by chemiluminescent microparticle immunoassay (CMIA) on the ARCHITECT i System (Diagnostic Range: 4 - 14.5%). The sample was incubated with pre-treatment reagent to lyse the red blood cells. Pre-treated sample was then incubated with magnetic micro particles with a silica surface. Hemoglobin

and HbA1c in the sample bind to the silica surface of the micro particles. Following a wash cycle, anti-HbA1c acridinium-labeled conjugate was added to create a reaction mixture. Following another wash cycle, pre-trigger(1.32%(w/v) hydrogen peroxide) and trigger solutions (0.35 N sodium hydroxide) are added to the reaction mixture. The resulting chemiluminescent reaction was measured as relative light units(RLUs).

The hemoglobin and HbA1c that are bound to the surface of the microparticles represent the total percentage present in the sample however, only the HbA1c result was required to determine the %HbA1c in the sample. A direct relationship exists between the amount of HbA1c in the sample and RLUs detected by the ARCHITECT i system optics.

The patients who had presented with infected wounds underwent an initial wound debridement with or without below ankle minor amputations as required for control of sepsis. The patients were imaged using Intra arterial digital subtraction angiography or magnetic resonance angiography or computerized tomography angiogram as appropriate. Patients were selected for EVT based on lesion suitability, operator expertise, associated co-morbdities and high risk for prolonged open surgeries.

Patients planned for EVT, received preoperative loading dose of Clopidogrel 300mg previous day and started on oral N- acetyl cysteiene 600mg orally for two days prior to procedure[75]. All DM patients who were on oral hypoglycemic agents were switched over to regular insulin and strict glycemic control was ensured peri operatively. Patients were started on IV hydration with 0.9% NaCl at 1 mL/kg/hr for 12 hours pre-procedure and 12 hours post-procedure[76] with 154mEq/L infusion of sodium bicarbonate as a bolus of 3 mL/kg/hour for 1 hour before the administration of contrast, followed by 1 mL/kg/hour for 6 hours during and after the procedure[76]. The procedures were carried out under local anesthesia with monitored anesthesia

care(MAC). All cases were done by consultant vascular surgeons with more than 10 years experience in EVT. The access was obtained either ipsilateral ante grade or retrograde contra lateral depending on lesion location. Usually 6Fr sheath was deployed and standard wire and catheter technique used to cross the lesion and the diseased segments were treated with angioplasty PTA balloons and secondary stenting of SFA was done at the discretion of the operator for flow-limiting dissections (grade C or higher)[77,78], intimal flaps, acute occlusions, or poor technical results (>30% residual stenosis). Nonionic contrast media Iopromide 300mg per ml (Ultravist®) or CO2 for CKD patients for imaging was used. Systemic heparinisation was done as soon an access was obtained; 80U/kg body weight and then 1000units IV for every passing hour. Activated Clotting Time (ACT) was used to keep track of the patient anticoagulation status for quick and efficient monitoring and was maintained at 250-300 seconds throughout the procedure.

Technical success was defined in terms of hemodynamic and clinical success. Hemodynamic success was defined as an ABI increase of at least 0.10 or improvement in plethysmographic tracing by at least 5 mm for patients with non compressible vessels. Clinical success was defined as an improvement of at least one clinical Rutherford classification category with demonstrable hemodynamic success for patients in category 4. Patients with tissue loss (categories 5 and 6) required an improvement to at least claudication and healing of their ulcers with confirmed improved hemodynamics[79,80].

After the procedure, the sheath was removed when the ACT was <180 seconds. Closure device or the manual compression was applied for 10mins or till there was no bleeding with continuous hemodynamic monitoring in the recovery room. The post procedure pulse/doppler signals status were noted and the PVR/ABI

were checked on the first post operative day. The hydration was continued for 12 hrs and N-acetyl cysteine for next 48 hours.. Any secondary procedures, planned or unplanned in the form of wound debridement/revision or minor amputations were recorded. Major amputations were defined as those above the ankle and minor as those below the ankle[81]. Post operative duplex ultrasound examination (using LOGIQ®e ©General Electric Company) was performed for each patient in an accredited vascular laboratory by and experienced sonographer.

All were started on aspirin 150mg OD if only angioplasty was done and clopidogrel 75mg and aspirin 150mg was given if a stent was deployed. If the patient was already on double antiplatelets, they were continued. All received atorvastatin 20mg HS for 6 months. Other medications for DM, hypertension and for any cardiac problems were continued as per treating physician's advice. The antibiotics, analgesics were prescribed as per patient and procedure requirements.

Depending upon the type of the wound, they were either dressed with hydrocolloids or vacuum assisted device was applied. All patients were counseled about the life style modification regarding the foot ware and foot care, with regular follow up as per our protocol.

Follow Up

All enrolled patients were followed postoperatively with thorough clinical examination and PVR/ABI surveillance at 1, 3, 6 and 9 months, which is consistent with our standard practice. The duplex ultrasound examination was performed if there was a worsening in their symptoms with an increase in one category in the Rutherford scale, decrease in ABI >0.15 from the maximum post procedural level or clinical worsening of tissue loss[82]. The duplex ultrasound examination was

performed in an accredited vascular laboratory by and experienced sonographer and a restenosis area was defined as an increase in peak systolic ratio ≥2.4[83]. Primary patency was defined as the duration of follow-up in which there is an absence of occlusion or significant restenosis within the treated segment[84].

Restenosis was defined as >50% decrease in post intervention luminal diameter seen on noninvasive imaging or angiography. A vessel was considered patent if it was free from occlusion/restenosis by noninvasive imaging or angiography, or both[63,79].

At 6 months of follow up, all the three inflammatory marker levels with HbA1c were repeated.

Statistical Analysis

The sample size needed to obtain significant differences with 80% degree of statistical power and a type error alpha of 0.05, was calculated on the basis of prior studies[10,50] analyzing plasma hsCRP and fibrinogen levels and their effects on primary patency rates [1--6, 12]. It was calculated to be a minimum of 30 patients.

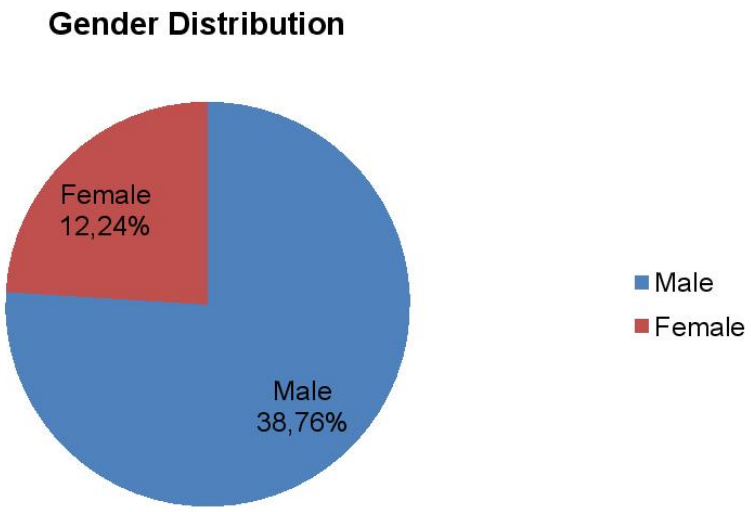
Statistical analysis was performed using SPSS, version 17.0 (SPSS, Chicago, IL). Percentages were computed based on complete data. Continuous variables were reported as mean ± standard deviation. Between-group differences in continuous variables were tested using unpaired Student t test (two tailed). Likewise, this test was performed in order to find statistical differences in basal inflammatory markers in patent and restenotic groups. A P value less than 0.05 was considered significant and value less than 0.001 as highly significant.

RESULTS

DEMOGRAPHY:

219 patients underwent lower limb revascularization for CLI from April 2013 to March 2014. 78 and 58 were excluded as they underwent bypass and hybrid procedures respectively. Out of 83 who underwent technically successful EVT, 33 were excluded based on other exclusion criteria. 50 patients were included in the study, of which 38 (76%) were males and 12 (24%) females. (Figure 3)

Figure 3: Gender Distribution



AGE

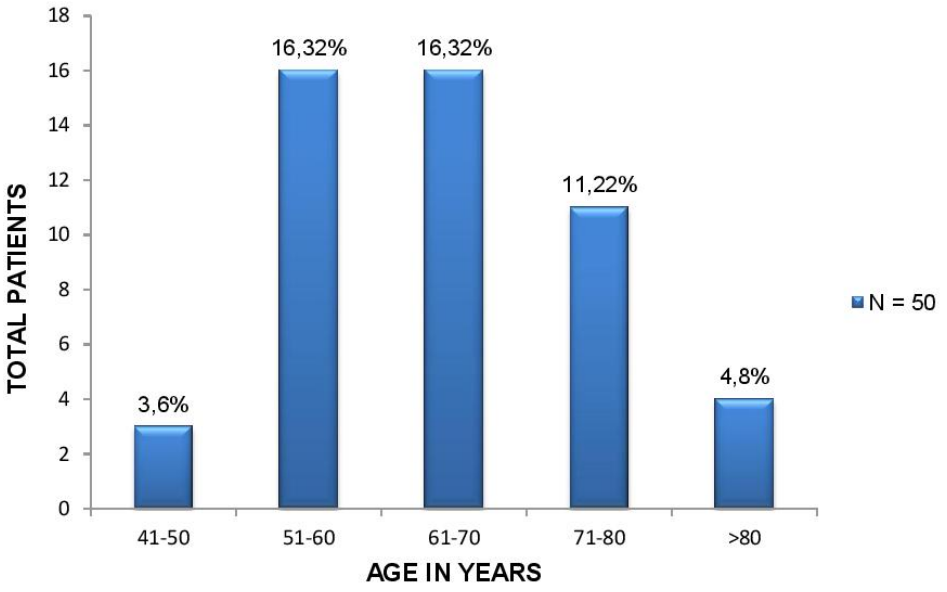
The mean age distribution was 65.4 ± 10.51 years with 64% of them between 51-70 years. Table 1 and Figure 4

Table1: Age Distribution

Age in years	Number of patients	%
41-50	3	6
51-60	16	32
61-70	16	32
71-80	11	22
>80	4	8

MEAN AGE: 65.4 ± 10.51 years

Figure 4: Age Distribution



CO-MORBIDITIES

On analyzing the co-morbidities, 44 (88%) were diabetics, 70% were hypertensive, 44% had history of CAD, 2% had CVD and 6% were known to have CKD. 16 (32%) were present smokers and 6 (12%) were ex-smokers with 28 (56%) of them having no history of smoking. (Table 2, Figure 5 and 6).

Table 2: Co Morbidities

Co morbidities	Number of patients (N=50)	%
Diabetes Mellitus	44	88
Hypertension	35	70
CAD	22	44
CVD	1	2
CKD	3	6

Figure 5: Co Morbidities Prevalence

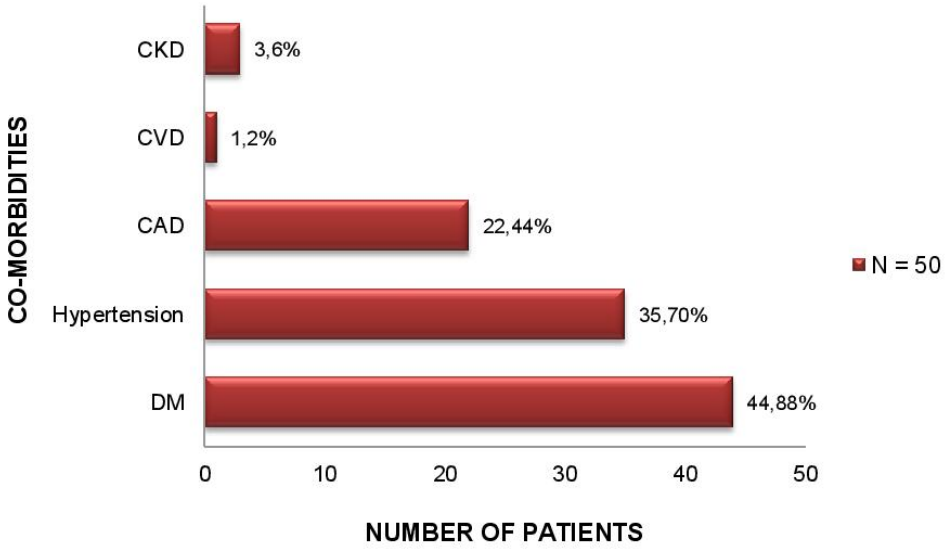
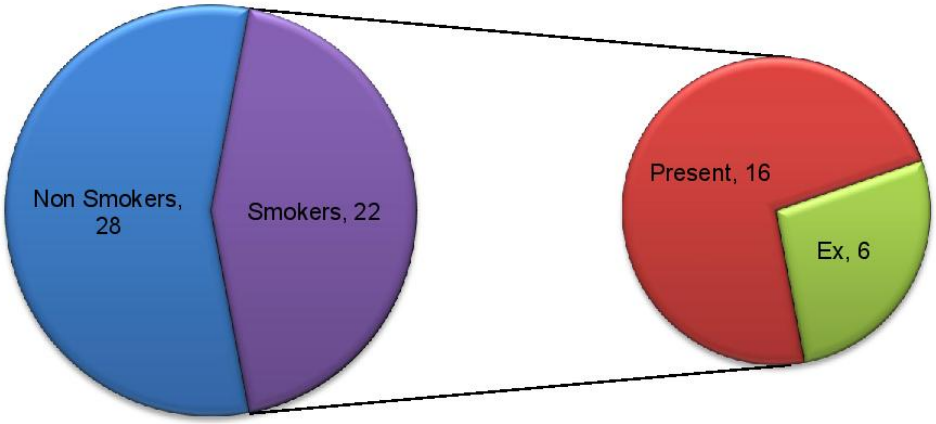


Figure 6: Prevalence of Smoking (N=50)



CLINICAL AND WOUND CLASSIFICATION

Patients were categorized according to Rutherford classification for chronic limb ischemia[69] (Table 3) and the wounds were categorized according to wound characteristic staging from WIFI classification(Wound characteristic, Ischemia, and Foot Infection)[73] (Table 4).

Among 50 patients, 5 (10%) were in Rutherford category 4, 27 (54%) in category 5 and 18 (36%) of them in category 6. According to wound characteristic staging, 5 patients belong to stage 0, 6 to stage 1, 33 in stage 2 and 6 in stage 3.

The hsCRP basal levels were categorized in relation to wound characteristic staging and then their respective means were compared with that of cohort mean of hsCRP to find out was there any significant difference between them. Cohort mean of hsCRP was 53.04±54.43 mg/L. Mean hsCRP for stage 0,1,2 and 3 were 13.8±6.4 mg/L; 40.7±69 mg/L; 49.5±46.27 mg/L and 111.18±67.3 mg/L respectively.

The mean hsCRP value of wound characteristic stage 1, 2 and 3 were not statistically different from the cohort mean of hsCRP ($p = 0.68$; $p = 0.66$; $p = 0.08$) (Table 5).

Table 3: Clinical Classification According To Rutherford Classification of Chronic Limb Ischemia

Category	Number of Patients (N=50)	%
4	5	10
5	27	54
6	18	36

Table 4: Wound Classification According To Wound Characteristic Staging In WIFI Classification[73]

Staging	Number of Patients (N=50)	%
0	5	10
1	6	12
2	33	66
3	6	12

Table 5: Comparison Of Different Wound Categories hsCRP With That of Cohort Mean

Wound grade	hsCRP(mg/L)	Cohort hsCRP(mg/L)	P
0	13.8±6.4	**53.04±54.53**	
1	40.7±69		0.68
2	49.5±46.27		0.66
3	111.18±67.3		0.08

Mean ± SD, Normal hsCRP <1mg/L

DISTRIBUTION OF LESIONS

Operative intervention was infra inguinal EVT consisting of angioplasty primarily and selective stenting as needed. Right and left lower limbs were nearly evenly involved (24 & 26 patients). 8 (16%) required only SFA, and 32 (64%) had infra popliteal interventions, 10 (20%) required multi-level corrections. Among the 8 patients with isolated SFA interventions 6 required stenting. The distribution in infra popliteal lesions were 0-TPT; 7- ATA; 6-PTA; 1-Peroneal and 18 were multi vessel lesions. Out of 10 who required multilevel correction 6 had SFA/Popliteal artery (PA) angioplasty with infra popliteal angioplasty and other 4 had SFA/PA angioplasty stenting with infra popliteal angioplasty (Table 6, Figure 7 and 8).

Table 6: Distribution of Lesions

Lesion Distribution	Number of Cases (50)
Superficial Femoral Artery(SFA)	**10 (16%)**
Angioplasty Alone	2
Angioplasty With Stenting	6
Infra popliteal	**32 (64%)**
Tibio Peroneal Trunk	0
Anterior Tibial Artery	7
Posterior Tibial Artery	6
Peroneal Artery	1
Multiple Vessel	18
Multilevel	**10 (20%)**
SFA/Popliteal Artery(PA) angioplasty + Infra popliteal angioplasty	6
SFA/PA angioplasty with stenting and Infra popliteal angioplasty	4

Figure 7: Distribution of Lesions

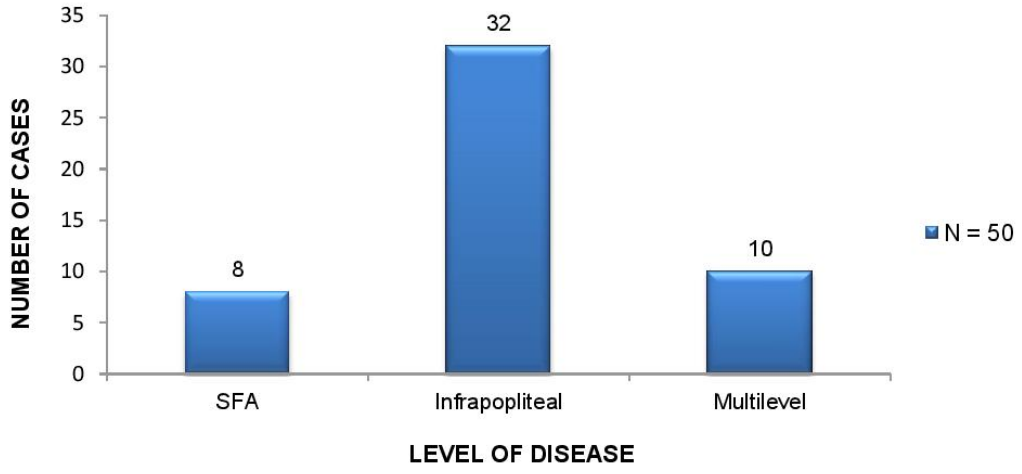
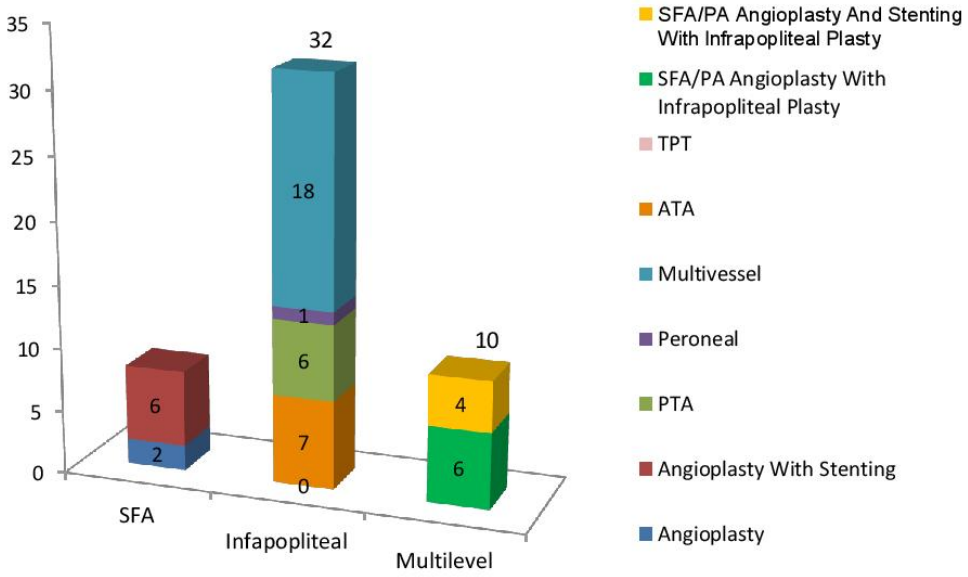


Figure 8: Arterial segment and Procedure Distribution



OUTCOMES OF ENDOVASCULAR THERAPY

Patients were analyzed according to primary patency on follow up at any time frame and were categorized in two groups. A) Restenosis group: Those with restenosis in treated vessel or progression of disease ; (B) Patent Group: The treated vessel is patent with no progression of disease on follow up of 9 months.

In this study of 50 patients, 17 (34%) patients had restenosis/ progression of disease. 14 among them were diabetics and 6 smokers (5 present, 1 ex smoker). Out of this 17, 5 had restenosis of treated segment, 8 had progression of disease in same vessel with restenosis of treated vessel and remaining 4 developed progressive disease at different level. Among 17, 65% (11) were treated non operatively with medical management only as they were asymptomatic and wound had healed; 4 patients underwent revascularization (symptom oriented target lesion revascularization(TLR)) and 2 patients had major amputations. Time to restenosis was 1 month for 2 patients; 3 months for 1 patient while 9 and 6 patients developed restenosis at 6th and 9th month of follow up respectively. One minor amputation (Trans metatarsal Amputation) was in patent group (Figure 9 and 10) (Table 7 and 8).

Figure 9: Time to Restenosis/Progression of Disease

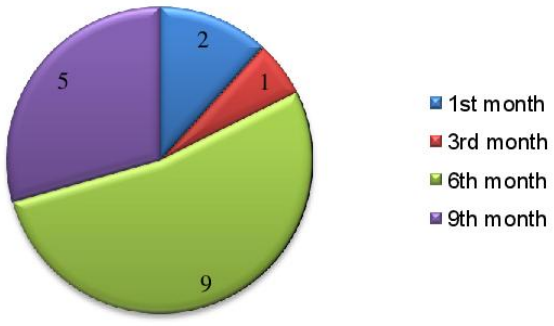


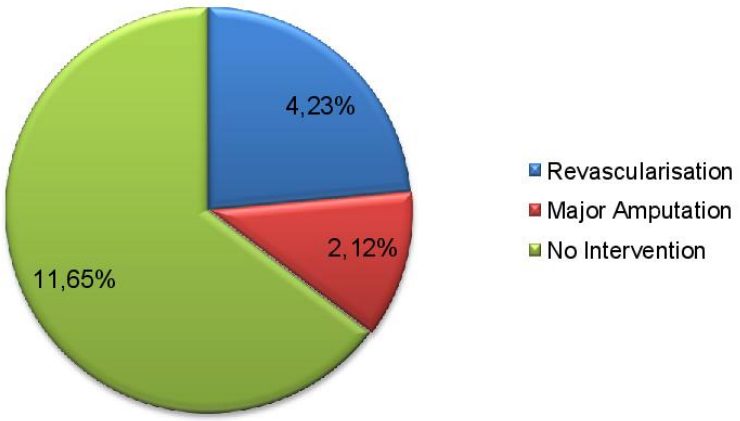
Table 7: Distribution of Restenosis/Progression of Disease

Restenosis/Progression of Disease	Number(N=17)
Restenosis	5
Progression Of Disease In Native Treated Vessel	8
Progression Of Disease At Different Level	4

Table 8: Management of Restenosis Group

Restenosis/Progression of Disease	Number (N=17)
Revascularization	4(23%)
No Re-Intervention	11(65%)
Major Amputation	2(12%)

Figure 10: Management of Restenosis Group



ROLE OF INFLAMMATORY MARKERS

The basal hsCRP and Lp(a) levels were significantly higher in restenosis group (114.98±48.66 mg/L; 67±88.5 mg/dl) in comparison to patent group (21.12±16.23 mg/L ; 31.31±24.4 mg/dl) of patients ($p < 0.0001$; $p = 0.03$) (Figure 11 and 13). The S. Fibrinogen was not significantly different in between two groups (331.03±66.03 mg/dl ; 342.65±84.71 mg/dl) ($p = 0.6$) (Figure 15)(Table 9).

Similarly, at 6 months of the follow up the hsCRP and Lp(a) remained significantly higher in restenosis group (7.7±10.01 mg/L; 31.43±28.22 mg/dl) in comparison to patent group (3±2.27 mg/L; 17.83±16.15 mg/dl) ($p = 0.01$; $p = 0.03$) (Figure 12 and 14). The S. Fibrinogen was not significantly different in between two groups at six months (299.09±76.71 mg/dl ; 332.88±91.52 mg/dl) ($p = 0.17$) (Figure 16)(Table 10).

While comparing Lp(a) basal levels with that of at 6 months follow up between patent (31.3±24.4 mg/dl; 17.8±16.15 mg/dl) and restenosis (67±88.5 mg/dl; 31.43±28.2 mg/dl) group respectively, the difference was decreased significantly in patent group but not in restenosis group at 6 months ($p = 0.01$; $p = 0.12$) (Figure 17 and 18)(Table 11).

All diabetic patients in restenosis group had HbA1c >7 with mean value decreased from pre operatively value of 8.2±1.64 to 7.1±0.8 postoperatively at 6months.

Table 9: Comparison of Basal Inflammatory Marker Levels Between Two Groups

Basal Levels	Patent Group	Restenosis Group	p
hsCRP(mg/L)	21.12±16.23	114.9±48.66	<0.0001
S. Fibrinogen(mg/dl)	331.03±66.03	342.65±84.71	0.6
Lp(a)(mg/dl)	31.31±24.4	67±88.5	0.03

mean ± SD

Table 10: Comparison of Inflammatory Marker Levels At 6 Months Between Two Groups

At 6 months	Patent Group	Restenosis Group	p
hsCRP(mg/L)	3±2.27	7.7±10.09	0.014
S. Fibrinogen(mg/dl)	299.09±76.71	332.88±91.52	0.17
Lp(a)(mg/dl)	17.83±16.15	31.4±28.2	0.03

mean ± SD

Table 11: Comparison Of Lp(a) Levels At Basal And 6 Months Between Two Groups

Lp(a)	Basal Levels (mg/dl)	At 6 Months(mg/dl)	p
Patent Group	31.31±24.4	17.83±16.15	0.01
Restenosis Group	67±88.5	31.4±28.2	0.12

mean ± SD

Figure 11 : Comparison Of Basal hsCRP Levels Between Two Groups With 95% Confidence Interval (CI) Error Bars

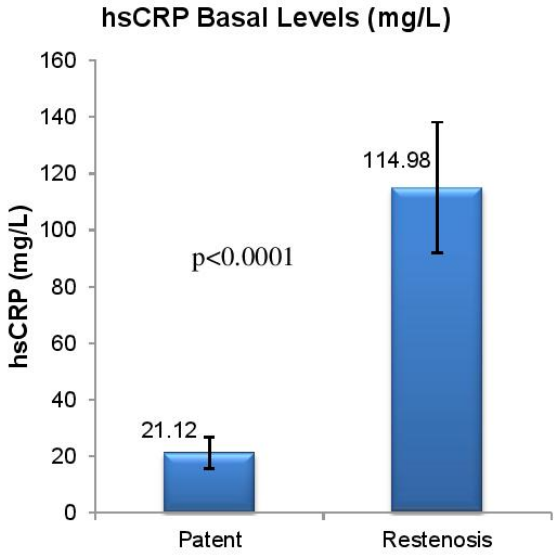


Figure 12: Comparison Of hsCRP Levels At 6 Months Between Two Groups With 95% CI

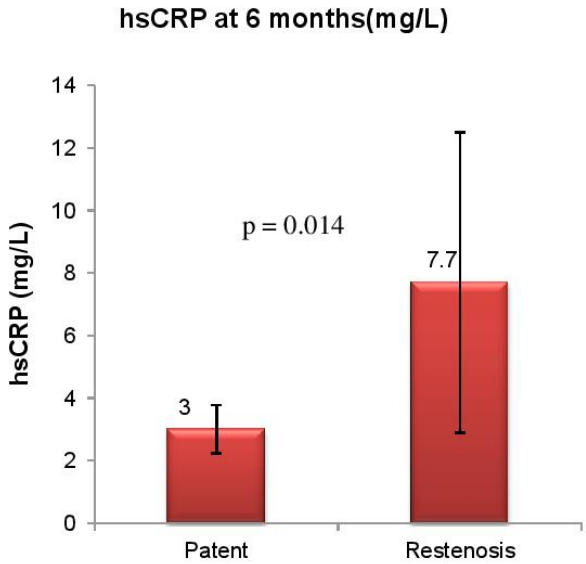


Figure 13: Comparison Of Basal Lp(a) Levels Between Two Groups With 95% CI

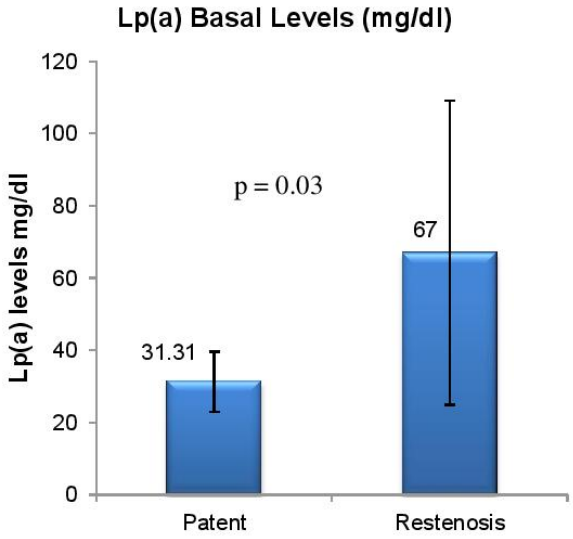


Figure 14: Comparison Of Lp(a) Levels At 6 Months Between Two Groups With 95% CI

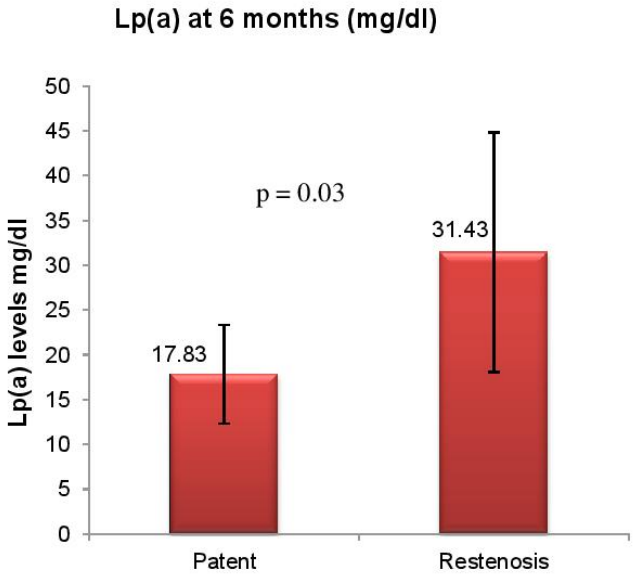


Figure 15: Comparison Of Basal S. Fibrinogen Levels Between Two Groups With 95% CI

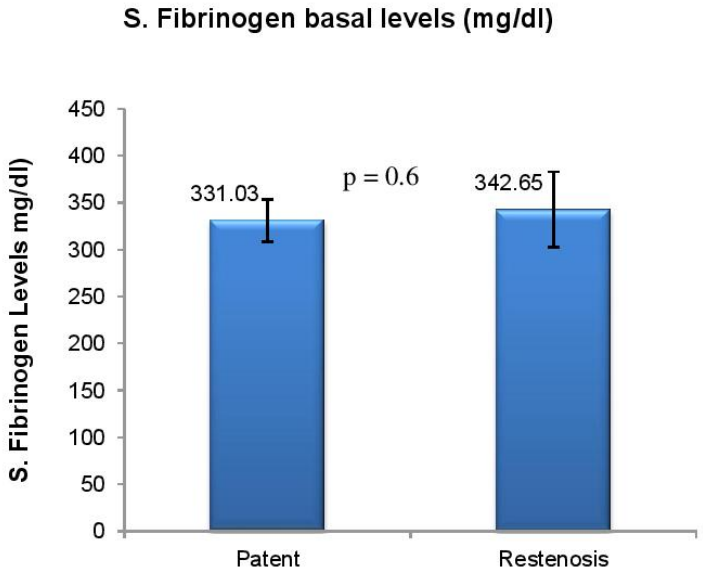


Figure 16: Comparison Of S. Fibrinogen Levels At 6 Months Between Two Groups With 95% CI

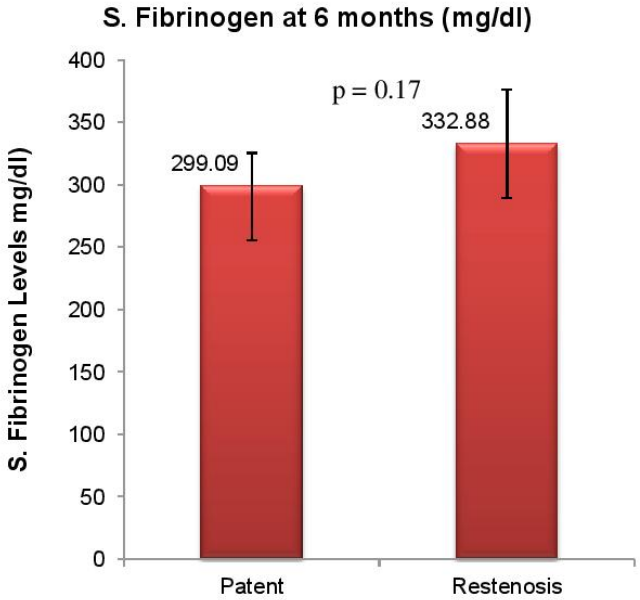


Figure 17: Comparison of Lp(a) Levels In Patent Group of Basal And At 6 Months With 95% CI

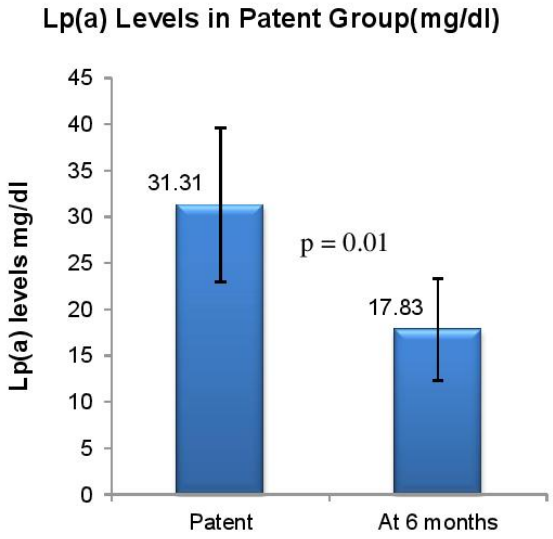
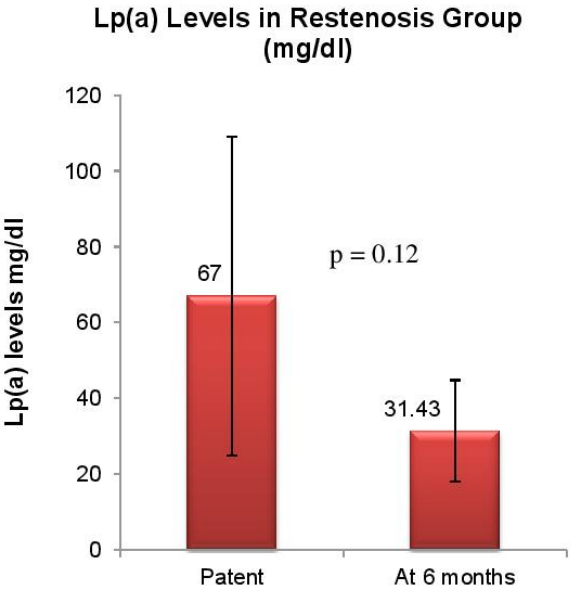


Figure 18: Comparison of Lp(a) Levels In Restenosis Group of Basal And At 6 Months With 95% CI



Total 7 patients lost to follow up with primary patency of 60.9% and limb salvage of 93.6% at 9 months. 3 patients died due to cardiac cause in course of follow up (1 at 6 months and 2 at 9 months). Of the 3 who died, two were from restenosis group and 1 from patent group.

DISCUSSION

PAD is a relatively common condition affecting up to 20% of the population older than 65 years and is becoming a growing health problem[85,86]. It is associated with a high cardiovascular morbidity and mortality[2] and in its symptomatic form represents an important cause of disability[87].

Because EVT is minimally invasive, unless a major bleeding complication occurs, it has become an accepted therapeutic alternative to open surgery in patients with PAD. Initial technical success rates for EVT are well accepted[48,88,89]. However, the percentage of reinterventions in these patients can be up to 40% in the first 6 months after the initial procedure. The exact causes of these early failures are not well understood. A previous study has shown that the initial inflammatory burden can prognosticate the need for long-term reintervention and mortality in these patients [57].

Vascular wall injury during balloon dilation of the coronary and peripheral arteries induces a perivascular inflammatory response[90,91,92]. The inflammatory process is a trigger for vascular SMC proliferation and constrictive neointimal formation and thus is involved in the pathogenesis of post angioplasty restenosis[90]. The pre procedure CRP level has also been reported to be a risk factor for restenosis after coronary angioplasty[93,94] and after PTA of the SFA[95,96]. The data suggest that the effect of the systemic inflammatory process on the results of EVT could be independent of the effect that the surgical procedure can have on the inflammatory process at the arterial wall[58].

Although the mechanisms of diabetic vascular disease remain incompletely understood, considerable data suggest that hyperglycemia itself causes vascular damage. Furthermore, the outcome of EVT in DM patients is not yet well known. Some authors have found no difference in outcomes for DM patients undergoing

EVT [67,97], whereas others have found worse results in these patients[41]. However, DM could be an increasingly important independent factor because of the rising number of PAD patients with DM.

Meanwhile, inflammatory markers from asymptomatic patients have shown to be risk factor for the development of subsequent PAD[98]. Moreover, hsCRP levels before and after intervention have been associated with 6-month restenosis rates after femoropopliteal angioplasty, finding a direct relationship between the inflammation triggered by the EVT itself and the risk of restenosis [50,82].

Previous studies have shown that the baseline CRP levels are predictors of adverse events after percutaneous coronary interventions independent of diabetic status[99,100] Primary prevention studies among healthy people have also shown significant cardiac risk prediction by means of elevated CRP levels without correlation to diabetes. These data appear to demonstrate that CRP levels predict cardiac risk independent of diabetic status[101].

The pathophysiological reason for an association between CRP and EVT prognosis is uncertain. However, data suggest that the effect of the systemic inflammatory process on the results of EVT could be independent of the effect that the surgical procedure can have on the inflammatory process at the arterial wall. Persistently elevated CRP levels may represent either an ongoing inflammatory process or the extension of atherosclerotic lesions in PAD. A growing body of evidence from human studies[102] indicates that inflammatory mechanisms contribute to the onset and extension of the PAD. Elevated CRP levels may also affect coagulation through the important role of tissue factor expression[103]. Thus, high CRP levels are implicated in both development and post-therapeutic prognosis in PAD.

Lp(a) is a heterogeneous macromolecule consisting of a LDL molecule that contains Apo B100 linked by a disulfide bridge to Apo A, which is a hydrophilic glycoprotein of the plasminogen family[32,33].

Lp(a) is less studied and its physiological role has not yet been entirely determined, but it is considered a cause of endothelial dysfunction[34]. Lp(a) has a high affinity for proteoglycans, which is probably why it is found in high amounts in atherosclerotic plaques[104]. High plasma levels of Lp(a) are strongly associated with CAD[105,106] stroke, and PAD[32,107]. Although many recent reports have also demonstrated a positive correlation between high serum Lp(a) levels (>30mg/dl) and restenosis after percutaneous coronary interventions[37,108] only Maca et al.[38,39] have reported a similar strong relationship between Lp(a) and restenosis after peripheral PTA of the femoropopliteal segment.

We compared our results with that of Bleda S et al [56], whose aim was to determine the effect of inflammatory preoperative burden on the incidence of reintervention and mortality after EVT and to investigate if DM has a bearing on these results. 143 patients were included in the above mentioned study who underwent EVT for Rutherford category 3, 4 and 5, of which 64.1% were diabetics and 57.9% smokers. Distribution of revascularized lesion areas included the iliac artery in 23 patients (16.1%), SFA in 66 (46.2%), PA in 8 (5.6%), infra popliteal in 16 (11.2%), and multilevel treatment in 30 (20.9%). In comparison, the present study had 50 patients who underwent EVT were under Rutherford category 4, 5 and 6 with 88% being diabetics and 44% smokers. The lesion distribution of lesions – 8 (16%) SFA intervention, 32 (64%) infra popliteal intervention and multilevel in 10 (20%) patients.

In the above mentioned study, 48 patients underwent reintervention (including target lesion revascularization (TLR - physiological driven and amputation), whereas only 4 patients required reintervention (TLR- clinically driven) out of 17 restenosis/progression of disease as 65% of them were treated conservatively on medical treatment as they were asymptomatic and wound had healed, in present study. In Bleda S et al[56] study, the basal levels of both hsCRP and S. Fibrinogen in reintervention group were significantly high ($p = 0.001$ and $p = 0.04$ respectively), in comparison to non-reintervention group. Also there was no statistically significant difference between DM and non-DM patients in the 1-year need of reintervention (33.3% versus 40.3%, $p = 0.15$, resp.). Similarly, in the present study hsCRP was significantly high at both basal and 6months follow up ($p = 0.0001$ and $p = 0.014$ resp.,) in restenosis group when compared to patent group. The S. Fibrinogen levels were not significantly different between two groups both at basal and at 6months follow up ($p = 0.6$ and $p = 0.17$ respectively).

Another study was conducted by Bleda S et al[58], to determine if CRP can predict the outcomes of lower extremity EVT in patients with PAD and to calculate a cutoff value that may be useful in identifying patients with a higher risk of EVT failure at 1 year. It was a 2 year study, with 121 patients enrolled in the initial 18 months under derivative set and another 53 patients under validation set enrolled in subsequent 6 months. Patients with Rutherford category 6 were excluded from both sets and 77.7% and 75.5% of the patients were with CLI in derivative and validation set respectively. The distribution of target lesions in both sets was not statistically significant. Of the 121 patients in derivative set 46 of them required reintervention within 1year and CRP levels were significantly elevated at baseline and 1month after the endovascular procedure ($p < 0.001$). There was not a significant association

between the incidence of reintervention and DM (HR 0.57, 95% CI 0.4 to 1.2; p=0.2). A greater incidence of secondary interventions was noted in patients with baseline CRP levels ≥9.8 mg/L (65.5% vs.29.3%, p<0.01). Similarly in validation set a pre-EVT CRP value ≥9.8 mg/L was significantly associated with a higher risk of secondary intervention (p = 0.009). Likewise, basal CRP levels were a strong independent prognostic marker of 1-year reintervention (HR 1.1; 95% CI 1.02 to 1.18; p=0.008), similar to that shown in the derivation set. According to study, the baseline CRP level can predict the need for secondary intervention at 1 year, and also CRP value at 1 month had a strong association with 1-year revascularization events.

In comparison, the present study had all patients with CLI of whom 17 required reintervention and hsCRP was significantly high both at pre-EVT and at 6 months follow up period in comparison to patent group(p = 0.0001 and p = 0.014 resp.). These findings are consistent with previous observations of elevated CRP values reflecting the severity and extent of PAD.

The pathophysiological reason for an association between CRP and EVT prognosis is uncertain. However, data suggest that the effect of the systemic inflammatory process on the results of EVT could be independent of the effect that the surgical procedure can have on the inflammatory process at the arterial wall. In present study, we have compared different wound category mean hsCRP levels with that of cohort mean and the independent group mean were not statistically significant from that of cohort mean (Table 12). So, we had comparable cohort of patients in all three groups in respect to wound category. It can be commented that systemic inflammatory process has independent effect on the results of EVT in comparison to surgical procedure.

Table 12: Comparison Of Different Wound Category(as per WIFI staging) hsCRP With That of Cohort

Wound grade	hsCRP(mg/L)	Cohort hsCRP(mg/L)	P
0	13.8±6.4		
1	40.7±69	**53.04±54.43**	0.68
2	49.5±46.27		0.66
3	111.18±67.3		0.08

mean ± SD

Previous studies have shown that the baseline CRP levels are predictors of adverse events after percutaneous coronary interventions independent of diabetic status[87,88]. Fournier JA et al[109] had commented that patients receiving a conventional stent, hsCRP values >2.5 mg/L at 30 days following the procedure seem to be associated with a greater incidence of late MACEs.

Rudofsky G et al[59], conducted the study to evaluate any correlation of fibrinogen and hematocrit with the early success of balloon angioplasty for PAD and compared the outcomes of angioplasty in diabetic and non-diabetic patients. In 3 years study period, 330 patients were enrolled of whom 109 were diabetics and 27.6% had CLI. The distribution of lesion was 10.9% iliac, 33.9% SFA, 8.8% infra popliteal and multilevel in 46.4% of patients. Fibrinogen concentrations significantly affected the angioplasty success rate ($p<0.03$) both prior to and following adjustment for PAD stage. Patients with failed angioplasty showed higher fibrinogen values compared with patients in whom the procedure was successful. Regardless of the PAD stage, diabetic and non-diabetic patients demonstrated approximately the same success rate for percutaneous catheter interventions in the study. As for patients

with severe PAD (stage IIbc/III/IV), diabetics showed significantly higher mean fibrinogen values ($p<0.044$) and lower mean hematocrit values ($p<0.022$) in cases of successful interventions compared with non-diabetics. In unsuccessful interventions, no significant differences were observed between non-diabetics and diabetics for either parameter. (Table 13)

Table 13: Fibrinogen and Hematocrit Values Following Successful and Failed Angioplasty in Advanced PAOD (Stages III/IV)

	Successful Angioplasty		**Failed Angioplasty**	
	Fibrinogen (mg/dl)	**Hematocrit, (%)**	**Fibrinogen (mg/dl)**	**Hematocrit,(%)**
Diabetics	504.3±183.8	36.8±5.1	515.8±202.3	36.3±6.4
Non diabetics	439.9±125.1	39.8±6.9	557.3±220.9	39.04±6.0

mean ± SD

In comparison, the present study included 50 patients among which 88% were diabetics and all of them had CLI with 8 (16%) cases required SFA intervention, 32(64%) cases had infrapopliteal intervention and multilevel treatment in 10 (20%)cases. The basal S. Fibrinogen levels in both patent and restenosis group was 331.03±66.03 mg/dl and 342.65±84.71 mg/dl respectively which was not statistically significant ($p = 0.6$). Even at 6 months the S. Fibrinogen levels were not significantly different in between two groups (299.09±26.17mg/dl ; 332.88±43.5mg/dl) ($p = 0.17$).

Giovanetti et al [60], conducted the study with the purpose to evaluate the influence of serum lipid subfraction concentrations on arterial patency after PTA in patients with infrainguinal PAD. It was a prospective study with 39 patients among whom 73.2% were diabetics and 90.3% were having CLI. The majority (34, 83%) of patients in the study had tibial lesions treated; more than half (26, 63%) had multi-segment treatment. They have documented the primary patency of 64.1% at 6 months, and showed that restenosis at 6 months was significantly related to HDL-C <40 mg/dL (HR 86.9, 95% CI 6.4 to 1183.1, p=0.001), LDL-C >100 mg/dL (HR 9.6, 95% CI 1.6 to 57.4, p=0.013), and Lp(a) >30 mg/dL (HR 6.1, 95% CI 1.4 to 26.3,p=0.016).

When comparing this cohort of the patients with our present cohort they were comparable as we had 88% diabetics and all with CLI and the results were quite comparable in terms of primary patency being 60.9% at 6 months. The restenosis group of patients had significantly higher Lp(a) both at pre EVT and at 6months in comparison to patent group (p = 0.03 and p = 0.03 resp.). (Table 14)

Table 14: Comparison Between Giovanetti et al And Present Study

Parameters	Giovanetti et al[9]	Present Study
Total Patients	39	50
Age(years)	68.6±10.1	65.4 ± 10.51
Diabetes	30(73%)	44(88%)
Critical Limb Ischemia	90.3%	100%
Primary Patency at 6 months	64.1%	60.9%
Lp(a)(>30mg/dl)	p = 0.016	p = 0.03 at pre EVT and 6months

Gary T et al [61], conducted a study to evaluate the association between plasma lipoproteins with the development of SFA in-stent restenosis and reocclusion in patients with PAD. 139 patients with PAD requiring secondary stent implantation in the SFA were included over 2 years period of which 35% were diabetics and 36% had CLI. 72 patients had developed restenosis over 12 months follow up period. In patients who had developed recurrence, the mean apo B level (105.8 ± 30.7 mg/dl) was significantly higher compared to patients with no recurrence (94.9 ± 29.7 mg/dl) ($P<0.05$). They demonstrated that increased levels of apo B were associated with the development of hemodynamically significant restenosis after stenting of the SFA within 1 year of follow-up.

In comparison, the present study has shown the similar results with significantly high levels of Lp(a) in restenosis group both at pre-EVT and at 6months in comparison to patent group of patients. ($p = 0.03$ and $p = 0.03$).

Studies to determine the effect of statins on Lp(a) levels have had mixed results [110-113]. With atorvastatin, Gonbert et al[114] found a significant reduction of Lp(a) levels using 10mg/day over a six-week period. A similar result was reported by van Wissen et al[113] in patients with familial hypercholesterolaemia taking 80mg of atorvastatin for 12 months. However, other authors have failed to find any effect of atorvastatin in lowering Lp(a) levels [115,116], and have even reported an increase [117] in the level of Lp(a).

Although the mechanisms by which atorvastatin reduces Lp(a) levels remain unclear, both lipid and non-lipid pathways may be involved. Lp(a) can be catabolized by the LDL receptor, but its affinity for the LDL receptor is considerably lower than that of LDL[118,119]. As previously demonstrated, LDL-cholesterol levels are independently related to Lp(a) concentrations[120], it is possible that the decrease in LDL cholesterol

with atorvastatin therapy contributes to the reduction in Lp(a) levels. However, in multivariate analyses, the decrease in Lp(a) was not associated with LDL-cholesterol reduction. In addition, there was a delayed decrease in Lp(a) (after 12 weeks of treatment) compared with reductions in LDL cholesterol (after four weeks of treatment). Thus, Hernandez C et al[110] suggested a direct inhibitory effect of atorvastatin on Apo(a) expression.

Hernandez C et al[110], conducted a study with an aim to determine the effect of atorvastatin therapy on plasma Lp(a) and biomarkers of inflammation in hypercholesterolaemic patients free of cardiovascular disease. It was a three-month randomized, double-blind, placebo-controlled trial in which 63 hypercholesterolaemic patients were randomly treated with either placebo or atorvastatin (10 or 40mg/day) for 12 weeks. Lp(a) and biomarkers of inflammation (CRP,IL-6 and -10, and tumor necrosis factor-alpha receptors [TNF-Rs]) were measured at study entry, and at four and 12 weeks of follow-up. At the end of follow up there was significantly low Lp(a) levels in patients on atorvastatin (10mg/day and 40mg/day) in comparison to them those who were on placebo. (10 [1–41]mg/dL versus 6 [1–38]mg/dL [p =0.02] and 21 [1–138]mg/dL versus 15 [1–103]mg/dL [p =0.04]. Their results suggest that 12-week of atorvastatin therapy is effective in reducing Lp(a) in dyslipidaemic patients free of CVD.

Wissen S et al [113], conducted a study to investigate Lp(a) concentrations in relation to statin treatment and the progression of atherosclerosis in a large cohort of familial hypercholesterolaemia (FH) patients. It was randomized and double blind trial with 325 patients included in study. At baseline, median Lp(a) concentrations were 327 mg/l and 531 mg/l in the atorvastatin and simvastatin arms, respectively (p = 0.03). In the atorvastatin arm, Lp(a) concentrations decreased to 243 mg/l after

one year ($p < 0.001$) and to 263 mg/l after two years ($p < 0.001$). In the simvastatin arm, Lp(a) concentrations decreased to 437 mg/l after one year ($p < 0.001$) and to 417 mg/l after two years ($p < 0.001$). The difference in Lp(a) reduction between the two treatment arms was significant after one year ($p = 0.004$), but not after two years ($p = 0.086$). They concluded that long term statin treatment significantly lowers Lp(a) in FH patients.

In comparison to both above studies, the present study shows that while comparing Lp(a) basal levels with that of at 6 months follow up between patent (31.3±8.32 mg/dl ; 17.8±5.51 mg/dl) and restenosis (67±42.07 mg/dl ; 31.43±13.4 mg/dl) group respectively, the difference was decreased significantly in patent group but not in restenosis group ($p = 0.01$; $p = 0.12$) with all the patients on atorvastatin 20mg for 6 months. There was a decreasing trend of Lp(a) levels in patients with restenosis from baseline (67±42.07 mg/dl) at 6months (31.43±13.4 mg/dl) but was not significant. This can be explained on the basis that the same dosage of atorvastatin may not be adequate for the patients with high basal Lp(a) levels. So, the dosage of atorvastatin should be individualized as per the patient's Lp(a) basal levels, but this should be assessed with a large cohort of the population study as our present study consist of small cohort.

O'Connor D et al [66], conducted the study to determine if the level of HbA1c has any effect on disease severity in diabetic patients with limb threatening ischemia. It was a retrospective analysis with 1year study period of 73 patients among whom 36 had HbA1c >7 and rest 37 had <7(mean 7.64 ± 2.04, range 5.1–14.7). They concluded that glucose control measured by HbA1c does not appear to affect severity of disease or need for reintervention in diabetics with limb threatening ischemia. This suggests other factors related to diabetes may play a role in

peripheral vascular disease. Larger, prospective studies are needed to assess the affect of glucose control in limb threatening ischemia. In present study, all diabetic patients who had restenosis were having HbA1c>7 and mean value decreased from 8.2±1.64 to 7.1±0.8 postoperatively at 6months.

The current study shows that baseline levels of hsCRP and Lp(a) are significant risk factors of a worse prognosis of EVT in patients with CLI with S. Fibrinogen being non significant marker of restenosis.

CONCLUSION

The inflammatory process plays a pivotal role in the pathogenesis and evolution of atherosclerosis as well as the development of its clinical manifestations as PAD. Persistently elevated hsCRP levels may represent either an ongoing inflammatory process or the extension of atherosclerotic lesions in PAD. Whether circulating hsCRP serves just a marker or plays a direct biologic role in lesion development remains an area of active investigation. All previous data suggest that the prognosis of EVT is marked by the previous inflammatory load. Data also suggests that the effect of the systemic inflammatory process on the results of EVT could be independent of the effect that the surgical procedure can have on the inflammatory process in the arterial wall.

In conclusion, as per the present study, baseline levels of hsCRP and Lp(a) are significant risk factors for restenosis in patients undergoing infra inguinal lower limb endovascular therapy for critical lower limb ischemia, S. Fibrinogen being a non significant marker of restenosis.

An imbalance in the lipid profile could be a major reason for the development of restenosis after revascularization in PAD patients. Lipid-lowering therapy and monitoring of lipid parameters should be considered in all PAD patients, especially after endovascular treatment. Various studies have determined the effect of statins on Lp(a) levels and many have also reported about reduction in Lp(a) levels by statins over longer period of treatment.

From the present study, we can infer that statin therapy dosage should be individualized according to the pre operative levels of Lp(a), but this should be assessed with a larger cohort of patients.

All diabetic patients who developed restenosis were having HbA1c levels >7. Moreover, DM patients are a heterogeneous group, and further investigation is required to understand better, the impact of DM on PAD and on the outcomes of EVT.

Multi centric studies with larger sample sizes are required to determine the value of these specific markers that will mandate us to take an aggressive medical therapy before undertaking EVT as the success of therapeutic procedure is determined and sustained by good medical management.

SUMMARY

We conducted a prospective, non randomized and single centre study to determine the effect of pre operative levels of hsCRP, S. Fibrinogen and Lp(a) on primary patency following technically successful EVT for infrainguinal PAD (Rutherford Category IV, V, VI)[69]. To summarize our results total 50 patients (38 males ; mean age of 65.4±10.5 years) underwent technically successful EVT of which 44(88%) were diabetics and 22(44%) being smokers. The mean hsCRP value of wound characteristic stage (WIFI classification) 1, 2 and 3 were not statistically different from the cohort mean of hsCRP ($p = 0.68$; $p = 0.66$; $p = 0.08$). Among 50 patients, 17 patients had (restenosis/ progression of disease) of which 5 had restenosis, 8 had progression of disease in same vessel with restenosis of treated vessel and rest 4 had developed progressive disease at different level. Among 17, 65% (11) were treated non operatively with medical management only as they were asymptomatic and wound got healed; 4 patients underwent revascularization and 2 patients ended up with major amputation with one had minor amputation in open group. 7 patients lost to follow up with primary patency of 60.9% and limb salvage of 93.6% at 9 months.

The basal hsCRP and Lp(a) levels were significantly higher in restenosis group in comparison to open group of patients ($p < 0.0001$; $p = 0.03$). The S. Fibrinogen was not significantly different in between two groups ($p = 0.6$).

Similarly, at 6 months of the follow up the hsCRP and Lp(a) remained significantly higher in restenosis group in comparison to open group ($p = 0.01$; $p = 0.03$). The S. Fibrinogen was not significantly different in between two groups at six months ($p = 0.17$).

While comparing Lp(a) basal levels with that of at 6 months follow up between open and restenosis group respectively, the difference was decreased significantly in open group but not in restenosis group at 6 months ($p = 0.01$; $p = 0.12$). There was a decreasing trend of Lp(a) levels in patients with restenosis from baseline (67±42.07 mg/dl) at 6months (31.43±13.4 mg/dl) but was not significant.

All diabetic patients in restenosis group had HbA1c >7 with mean value decreased from pre operatively value of 8.2±1.64 to 7.1±0.8 postoperatively at 6months.

Thus we conclude that baseline levels of hsCRP and Lp(a) are significant risk factors for restenosis in patients undergoing infrainguinal lower limb EVT for CLI , S. Fibrinogen being a non significant marker of restenosis. Also we can infer that statin therapy dosage should be individualized according to the pre operative levels of Lp(a), but this should be assessed with a larger cohort of patients. Finally, we will like to recommend regarding the measurement of these specific markers that will mandate us to take an aggressive medical therapy before undertaking EVT as the success of therapeutic procedure is determined and sustained by good medical management.

REFERENCES

1. Criqui MH. Peripheral arterial disease--epidemiological aspects. Vasc Med.2001;6(3 Suppl):3-7.
2. Premalatha G, Shanthirani S, Deepa R, Markovitz J, Mohan V. Prevalence and risk factors of peripheral vascular disease in a selected South Indian population: the Chennai Urban Population Study. Diabetes Care. 2000 Sep;23(9):1295-300.
3. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med. 1992 Feb 6;326(6):381-6.
4. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999 Jan;340(2):115-26.
5. Szmitko PE, Wang CH, Weisel RD, de Almeida JR, Anderson TJ, Verma S. New markers of inflammation and endothelial cell activation: Part I. Circulation. 2003 Oct 21;108(16):1917-23.
6. Boamponsem AG, Boamponsem LK. The role of inflammation in atherosclerosis. Adv. Appl. Sci. Res., 2011, 2 (4):194-207
7. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation. 1998 Feb 10;97(5):425-8.
8. Van Loon JE, de Maat MP, Deckers JW, van Domburg RT, Leebeek FW. Prognostic markers in young patients with premature coronary heart disease. Atherosclerosis. 2012 Sep;224(1):213-7.
9. Volanakis JE. Human C-reactive protein: expression, structure, and function. Mol Immunol. 2001 Aug;38(2-3):189-97.

10. Owens CD, Ridker PM, Belkin M, Hamdan AD, Pomposelli F, Logerfo F et al. Elevated C-reactive protein levels are associated with postoperative events in patients undergoing lower extremity vein bypass surgery. J Vasc Surg. 2007 Jan;45(1):2-9
11. Rossi E, Biasucci LM, Citterio F, Pelliccioni S, Monaco C, Ginnetti F et al. Risk of myocardial infarction and angina in patients with severe peripheral vascular disease: predictive role of C-reactive protein. Circulation. 2002 Feb 19;105(7):800-3
12. Verma S, Wang CH, Li SH, Dumont AS, Fedak PW, Badiwala MV et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation. 2002 Aug 20;106(8):913-9
13. Verma S, Li SH, Badiwala MV, Weisel RD, Fedak PW, Li RK et al. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. Circulation. 2002 Apr 23;105(16):1890-6.
14. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation. 2000 Oct 31;102(18):2165-8.
15. Pasceri V, Cheng JS, Willerson JT, Yeh ET. Modulation of C-reactive protein-mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. Circulation. 2001 May 29;103(21):2531-4.
16. Verma S, Badiwala MV, Weisel RD, Li SH, Wang CH, Fedak PW et al. C-reactive protein activates the nuclear factor-kappaB signal transduction pathway in saphenous vein endothelial cells: implications for atherosclerosis and restenosis. J Thorac Cardiovasc Surg. 2003 Dec;126(6):1886-91

17. Verma S, Kuliszewski MA, Li SH, Szmitko PE, Zucco L, Wang CH et al. C-reactive protein attenuates endothelial progenitor cell survival, differentiation, and function: further evidence of a mechanistic link between C-reactive protein and cardiovascular disease. Circulation. 2004 May 4;109(17):2058-67.
18. Szmitko PE, Fedak PW, Weisel RD, Stewart DJ, Kutryk MJ, Verma S. Endothelial progenitor cells: new hope for a broken heart. Circulation. 2003 Jun 24;107(24):3093-100.
19. Verma S, Szmitko PE, Yeh ET. C-reactive protein: structure affects function.Circulation. 2004 Apr 27;109(16):1914-7.
20. Wang CH, Li SH, Weisel RD, Fedak PW, Dumont AS, Szmitko P et al. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. Circulation. 2003 Apr 8;107(13):1783-90.
21. Li SH, Szmitko PE, Weisel RD, Wang CH, Fedak PW, Li RK et al.C-reactive protein upregulates complement-inhibitory factors in endothelial cells. Circulation. 2004 Feb 24;109(7):833-6.
22. Cheshire NJ, Wolfe JH, Barradas MA, Chambler AW, Mikhailidis DP. Smoking and plasma fibrinogen, lipoprotein (a) and serotonin are markers for postoperative infrainguinal graft stenosis. Eur J Vasc Endovasc Surg. 1996 May;11(4):479-86.
23. Wilhelmsen L, Svardsudd K, Korsan-Bengtsen K, Larsson B, Welin L, Tibblin G. Fibrinogen as a risk factor for stroke and myocardial infarction. N Engl J Med. 1984 Aug 23;311(8):501-5.
24. Naito M, Hayashi T, Kuzuya M, Funaki C, Asai K, Kuzuya F. Fibrinogen is chemotactic for vascular smooth muscle cells. FEBS Lett. 1989 Apr 24;247(2):358-60.

25. Naito M, Hayashi T, Kuzuya M, Funaki C, Asai K, Kuzuya F. Effects of fibrinogen and fibrin on the migration of vascular smooth muscle cells in vitro. Atherosclerosis. 1990 Jul;83(1):9-14.
26. Cook NS, Ubben D. Fibrinogen as a major risk factor in cardiovascular disease. Trends Pharmacol Sci. 1990 Nov;11(11):444-51.
27. Smith EB. Fibrinogen, fibrin and fibrin degradation products in relation to atherosclerosis. Clin Haematol. 1986 May;15(2):355-70.
28. Naito M, Funaki C, Hayashi T, Yamada K, Asai K, Yoshimine N et al. Substrate-bound fibrinogen, fibrin and other cell attachment-promoting proteins as a scaffold for cultured vascular smooth muscle cells. Atherosclerosis. 1992 Oct;96(2-3):227-34.
29. Sandkamp M, Funke H, Schulte H, Kohler E, Assmann G. Lipoprotein(a) is an independent risk factor for myocardial infarction at a young age. Clin Chem. 1990 Jan;36(1):20-3.
30. Ghilain JM, Parfonry A, Kozyreff V, Heller FR. Lipoprotein(a), cholesterol and coronary heart diseases. Lancet. 1988 Oct 22;2(8617):963.
31. Cheng SW, Ting AC, Wong J. Lipoprotein (a) and its relationship to risk factors and severity of atherosclerotic peripheral vascular disease. Eur J Vasc Endovasc Surg. 1997 Jul;14(1):17-23.
32. Jones GT, van Rij AM, Cole J, Williams MJ, Bateman EH, Marcovina SM et al. Plasma lipoprotein(a) indicates risk for 4 distinct forms of vascular disease. Clin Chem. 2007 Apr;53(4):679-85.

33. Scanu AM. Lipoprotein(a) and the atherothrombotic process: mechanistic insights and clinical implications. Curr Atheroscler Rep. 2003 Mar;5(2):106-13.
34. Schlaich MP, John S, Langenfeld MR, Lackner KJ, Schmitz G, Schmieder RE. Does lipoprotein(a) impair endothelial function? J Am Coll Cardiol. 1998 Feb;31(2):359-65.
35. Sotiriou SN, Orlova VV, Al-Fakhri N, Ihanus E, Economopoulou M, Isermann B et al. Lipoprotein(a) in atherosclerotic plaques recruits inflammatory cells through interaction with Mac-1 integrin. FASEB J. 2006 Mar;20(3):559-61.
36. Kamitani T, Taniguchi T, Miyai N, Kawasaki T, Kawasaki S, Sugihara H. Association between plasma lipoprotein(a) concentration and restenosis after stent implantation. Circ J. 2005 Jun;69(6):644-9.
37. Desmarais RL, Sarembock IJ, Ayers CR, Vernon SM, Powers ER, Gimple LW. Elevated serum lipoprotein(a) is a risk factor for clinical recurrence after coronary balloon angioplasty. Circulation. 1995 Mar 1;91(5):1403-9.
38. Maca T, Ahmadi R, Derfler K, Horl WH, Koppensteiner R, Minar E et al. Elevated lipoprotein(a) and increased incidence of restenosis after femoropopliteal PTA. Rationale for the higher risk of recurrence in females? Atherosclerosis. 1996 Nov 15;127(1):27-34.
39. Maca TH, Ahmadi R, Derfler K, Ehringer H, Gschwandtner ME, Horl W et al. Influence of lipoprotein(a) on restenosis after femoropopliteal percutaneous transluminal angioplasty in Type 2 diabetic patients. Diabet Med. 2002 Apr;19(4):300-6.
40. Al-Delaimy WK, Merchant AT, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Effect of type 2 diabetes and its duration on the risk of peripheral arterial disease among men. Am J Med. 2004 Feb 15;116(4):236-40.

41. Abularrage CJ, Conrad MF, Hackney LA, Paruchuri V, Crawford RS, Kwolek CJ et al. Long-term outcomes of diabetic patients undergoing endovascular infrainguinal interventions. J Vasc Surg. 2010 Aug;52(2):314-22.
42. Martindale JL, Holbrook NJ. Cellular response to oxidative stress: signaling for suicide and survival. J Cell Physiol. 2002 Jul;192(1):1-15.
43. Colwell J. Pathogenesis of vascular disease. Diabetes Obes Metab. 2000 Nov;2 Suppl 2:S19-24.
44. Krishnamurti U, Steffes MW. Glycohemoglobin: a primary predictor of the development or reversal of complications of diabetes mellitus. Clin Chem.2001;47(7):1157-65.
45. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med. 2004 Sep 21;141(6):413-20.
46. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53
47. Gordon IL, Conroy RM, Arefi M, Tobis JM, Stemmer EA, Wilson SE. Three-year outcome of endovascular treatment of superficial femoral artery occlusion. Arch Surg. 2001 Feb;136(2):221-8.
48. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007 Jan;45 Suppl S:S5-67.

49. Pozzi Mucelli F, Fisicaro M, Calderan L, Malacrea M, Mazzone C, Cattin L et al. Percutaneous revascularization of femoropopliteal artery disease: PTA and PTA plus stent. Results after six years' follow-up. Radiol Med. 2003 Apr;105(4):339-49.

50. Schillinger M, Exner M, Mlekusch W, Haumer M, Rumpold H, Ahmadi R et al. Endovascular revascularization below the knee: 6-month results and predictive value of C-reactive protein level. Radiology. 2003 May;227(2):419-25.

51. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation. 1998 Feb 10;97(5):425-8.

52. Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD, Fowkes FG. C-reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population: Edinburgh Artery Study. Circulation. 2005 Aug 16;112(7):976-83.

53. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA. 2001 May 16;285(19):2481-5.

54. Van Der Meer IM, De Maat MP, Hak AE, Kiliaan AJ, Del Sol AI, Van Der Kuip DA et al. C-reactive protein predicts progression of atherosclerosis measured at various sites in the arterial tree: the Rotterdam Study. Stroke. 2002 Dec;33(12):2750-5.

55. Musicant SE, Taylor LM Jr, Peters D, Schuff RA, Urankar R, Landry GJ et al. Prospective evaluation of the relationship between C-reactive protein, D-dimer and progression of peripheral arterial disease. J Vasc Surg. 2006 Apr;43(4):772-80

56. Bleda S, Haro J, Varela C, Lopez de Maturana I, Rodriguez J and Acin J. "Inflammatory Burden but Not Diabetes Mellitus Influences in Prognosis of Endovascular Revascularization in Peripheral Arterial Disease," ISRN Vascular Medicine, vol. 2013, Article ID 219479, 7 pages, 2013.

57. Bleda S, De Haro J, Acin F, Varela C, Esparza L, Lopez de Maturana I. Inflammatory Burden Predicts Long-Term Outcomes in Endovascular Therapy in Peripheral Arterial Disease. Ann Vasc Surg. 2013 Feb 9:27(4):459-66.

58. Bleda S, de Haro J, Varela C, Acin F. C-reactive protein and endovascular treatment of lower limb peripheral artery disease: an independent prognostic factor. J Endovasc Ther. 2015 Apr;22(2):233-9.

59. Rudofsky G, Strubel G, Michler E, Kuegler C, Biro F. Influence of fibrinogen and hematocrit on the early outcome of angioplasty in patients with PAOD. J Endovasc Ther. 2004 Apr;11(2):125-31.

60. Giovanetti F, Gargiulo M, Laghi L, D'Addato S, Maioli F, Muccini N et al. Lipoprotein(a) and other serum lipid subfractions influencing primary patency after infrainguinal percutaneous transluminal angioplasty. J Endovasc Ther. 2009 Jun;16(3):389-96.

61. Gary T, Rief P, Stojakovic T, Froehlich H, Scharnagl H, Hafner F et al. Lipoproteins and the development of restenosis after stent implantation in the superficial femoral artery in patients with peripheral artery disease. Cardiovasc Intervent Radiol. 2011 Aug;34(4):739-43.

62. Awad S, Karkos CD, Serrachino-Inglott F, Cooper NJ, Butterfield JS, Ashleigh R et al. The impact of diabetes on current revascularisation practice and clinical outcome in patients with critical lower limb ischaemia. Eur J Vasc Endovasc Surg. 2006 Jul;32(1):51-9.

63. Bakken AM, Palchik E, Hart JP, Rhodes JM, Saad WE, Davies MG. Impact of diabetes mellitus on outcomes of superficial femoral artery endoluminal interventions. J Vasc Surg. 2007 Nov;46(5):946-58

64. DeRubertis BG, Pierce M, Ryer EJ, Trocciola S, Kent KC, Faries PL. Reduced primary patency rate in diabetic patients after percutaneous intervention results from more frequent presentation with limb-threatening ischemia. J Vasc Surg. 2008 Jan;47(1):101-8.

65. Dick F, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. J Vasc Surg. 2007 Apr;45(4):751-61.

66. O'Connor DJ, Gargiulo NJ, Jang J. Hemoglobin A1c as a measure of disease severity and outcome in limb threatening ischemia. J Surg Res. 2012 May 1;174(1):29-32.

67. Surowiec SM, Davies MG, Eberly SW, Rhodes JM, Illig KA, Shortell CK et al. Percutaneous angioplasty and stenting of the superficial femoral artery. J Vasc Surg. 2005 Feb;41(2):269-78.

68. Abularrage CJ, Conrad MF, Hackney LA, Paruchuri V, Crawford RS, Kwolek CJ et al. Long-term outcomes of diabetic patients undergoing endovascular infrainguinal interventions. J Vasc Surg. 2010 Aug;52(2):314-22

69. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997 Sep;26(3):517-38.

70. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2000 Jan;23 Suppl 1:S4-19.

71. Verdecchia P, Angeli F. The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the weapons are ready. Rev Esp Cardiol. 2003 Sep;56(9):843-7.

72. Ferrer R, Hernandez Jara J. Chronic renal insufficiency. I: Definition, clinical course stages, progression mechanisms, etiology, and diagnostic criteria. Nefrologia 2001;21 Suppl 5:18-20.

73. Cull DL, Manos G, Hartley MC, Taylor SM, Langan EM, Eidt JF et al. An early validation of the Society for Vascular Surgery lower extremity threatened limb classification system. J Vasc Surg. 2014 Dec;60(6):1535-41.

74. Levine DM, Sloan BJ, Donner JE, Lorenz JD, Heinzerling RH. Automated measurement of lipoprotein(a) by immunoturbidimetric analysis. Int J Clin Lab Res. 1992;22(3):173-8.

75. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med. 2000 Jul 20;343(3):180-4.

76. Freeman RV, O'Donnell M, Share D, Meengs WL, Kline-Rogers E, Clark VL et al. Nephropathy requiring dialysis after percutaneous coronary intervention and the critical role of an adjusted contrast dose. Am J Cardiol. 2002 Nov 15;90(10):1068-73.

77. Huber MS, Mooney JF, Madison J, Mooney MR. Use of a morphologic classification to predict clinical outcome after dissection from coronary angioplasty. Am J Cardiol. 1991 Aug 15;68(5):467-71.

78. Tepe G, Zeller T, Schnorr B, Claussen CD, Beschorner U, Brechtel K et al. High-grade, non-flow-limiting dissections do not negatively impact long-term outcome after paclitaxel-coated balloon angioplasty: an additional analysis from the THUNDER study. J Endovasc Ther. 2013 Dec;20(6):792-800.

79. Rutherford RB. Reporting standards for endovascular surgery: should existing standards be modified for newer procedures? Semin Vasc Surg. 1997 Dec;10(4):197-205.

80. Conrad MF, Crawford RS, Hackney LA, Paruchuri V, Abularrage CJ, Patel VI et al. Endovascular management of patients with critical limb ischemia. J Vasc Surg. 2011 Apr;53(4):1020-5.

81. Rayman G, Krishnan ST, Baker NR, Wareham AM, Rayman A. Are we underestimating diabetes-related lower-extremity amputation rates? Results and benefits of the first prospective study. Diabetes Care. 2004 Aug;27(8):1892-6.

82. Schillinger M, Haumer M, Schlerka G, Mlekusch W, Exner M, Ahmadi R et al. Restenosis after percutaneous transluminal angioplasty in the femoropopliteal segment: the role of inflammation. J Endovasc Ther. 2001 Oct;8(5):477-83.

83. Ranke C, Creutzig A, Alexander K. Duplex scanning of the peripheral arteries: correlation of the peak velocity ratio with angiographic diameter reduction. Ultrasound Med Biol. 1992;18(5):433-40.

84. Ravin RA, Faries PL. Infrainguinal Disease: Endovascular Treatment. Cronenwett JL, Johnston KW (ed). Rutherford's vascular surgery, 8 ed. Philadelphia: Elsevier Saunders; 2014. pp. 1784.

85. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly: The Rotterdam Study. Arterioscler Thromb Vasc Biol. 1998 Feb;18(2):185-92.

86. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. Am Heart J. 2002 Jun;143(6):961-5.

87. Barletta G, Perna S, Sabba C, Catalano A, O'Boyle C, Brevetti G. Quality of life in patients with intermittent claudication: relationship with laboratory exercise performance. Vasc Med. 1996;1(1):3-7.

88. Lenti M, Cieri E, De Rango P, Pozzilli P, Coscarella C, Bertoglio C et al. Endovascular treatment of long lesions of the superficial femoral artery: results from a multicenter registry of a spiral, covered polytetrafluoroethylene stent. J Vasc Surg. 2007 Jan;45(1):32-9.

89. Vogel TR, Shindelman LE, Nackman GB, Graham AM. Efficacious use of nitinol stents in the femoral and popliteal arteries. J Vasc Surg. 2003 Dec;38(6):1178-84.

90. Schillinger M, Exner M, Mlekusch W, Haumer M, Ahmadi R, Rumpold H et al. Balloon angioplasty and stent implantation induce a vascular inflammatory reaction. J Endovasc Ther. 2002 Feb;9(1):59-66.

91. Serrano CV Jr, Ramires JA, Venturinelli M, Arie S, D'Amico E, Zweier JL et al. Coronary angioplasty results in leukocyte and platelet activation with adhesion molecule expression. Evidence of inflammatory responses in coronary angioplasty. J Am Coll Cardiol. 1997 May;29(6):1276-83.

92. Azar RR, McKay RG, Kiernan FJ, Seecharran B, Feng YJ, Fram DB et al. Coronary angioplasty induces a systemic inflammatory response. Am J Cardiol.1997 Dec 1;80(11):1476-8.

93. Buffon A, Liuzzo G, Biasucci LM, Pasqualetti P, Ramazzotti V, Rebuzzi AG et al. Preprocedural serum levels of C-reactive protein predict early complications and late restenosis after coronary angioplasty. J Am Coll Cardiol.1999 Nov 1;34(5):1512-21.

94. Blum A, Kaplan G, Vardinon N, Yust I, Burke M, Laniado S et al. Serum amyloid type A may be a predictor of restenosis. Clin Cardiol. 1998 Sep;21(9):655-8.

95. Tschopl M, Tsakiris DA, Marbet GA, Labs KH, Jager K. Role of hemostatic risk factors for restenosis in peripheral arterial occlusive disease after transluminal angioplasty. Arterioscler Thromb Vasc Biol. 1997 Nov;17(11):3208-14.

96. Schillinger M, Exner M, Mlekusch W, Rumpold H, Ahmadi R, Sabeti S et al. Vascular inflammation and percutaneous transluminal angioplasty of the femoropopliteal artery: association with restenosis. Radiology. 2002 Oct;225(1):21-6.

97. Costanza MJ, Queral LA, Lilly MP, Finn WR. Hemodynamic outcome of endovascular therapy for TransAtlantic InterSociety Consensus type B femoropopliteal arterial occlusive lesions. J Vasc Surg. 2004 Feb;39(2):343-50.

98. Engstrom G, Site-Flondell D, Lindblad B, Janzon L, Lindgarde F. Risk of treatment of peripheral arterial disease is related to inflammation sensitive plasma proteins: a prospective cohort study. J Vasc Surg. 2004 Dec;40(6):1101-5.

99. Choi DH, Park KW, Yang HM, Lee HY, Park JS, Kang HJ et al. Renal dysfunction and high levels of hsCRP are additively associated with hard endpoints after percutaneous coronary intervention with drug eluting stents. Int J Cardiol. 2011 Jun 2;149(2):174-81.

100. Delhaye C, Sudre A, Lemesle G, Marechaux S, Broucqsault D, Hennache B et al. Preprocedural high-sensitivity C-reactive protein predicts death or myocardial infarction but not target vessel revascularization or stent thrombosis after percutaneous coronary intervention. Cardiovasc Revasc Med. 2009 Jul-Sep;10(3):144-50.

101. Biondi-Zoccai GG, Abbate A, Liuzzo G, Biasucci LM. Atherothrombosis, inflammation, and diabetes. J Am Coll Cardiol. 2003 Apr 2;41(7):1071-7.

102. Vainas T, Stassen FR, de Graaf R, Twiss EL, Herngreen SB, Welten RJ, van den Akker LH, van Dieijen-Visser MP, Bruggeman CA, Kitslaar PJ. C-reactive protein in peripheral arterial disease: relation to severity of the disease and to future cardiovascular events. J Vasc Surg. 2005 Aug;42(2):243-51.

103. Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. Blood. 1993 Jul 15;82(2):513-20.

104. Bihari-Varga M, Gruber E, Rotheneder M, Zechner R, Kostner GM. Interaction of lipoprotein Lp(a) and low density lipoprotein with glycosaminoglycans from human aorta. Arteriosclerosis. 1988 Nov-Dec;8(6):851-7.

105. Luc G, Bard JM, Arveiler D, Ferrieres J, Evans A, Amouyel P et al. Lipoprotein (a) as a predictor of coronary heart disease: the PRIME Study. Atherosclerosis. 2002 Aug;163(2):377-84.

106. Suk Danik J, Rifai N, Buring JE, Ridker PM. Lipoprotein(a), measured with an assay independent of apolipoprotein(a) isoform size, and risk of future cardiovascular events among initially healthy women. JAMA. 2006 Sep 20;296(11):1363-70.

107. Milionis HJ, Filippatos TD, Loukas T, Bairaktari ET, Tselepis AD, Elisaf MS. Serum lipoprotein(a) levels and apolipoprotein(a) isoform size and risk for first-ever acute ischaemic nonembolic stroke in elderly individuals. Atherosclerosis. 2006 Jul;187(1):170-6.

108. Horie H, Takahashi M, Izumi M, Takaoka A, Fujita T, Sakamoto T et al. Association of an acute reduction in lipoprotein(a) with coronary artery restenosis after percutaneous transluminal coronary angioplasty. Circulation. 1997 Jul 1;96(1):166-73.

109. Fournier JA, Delgado-Pecellin C, Cayuela A, Cabezon S, Mendoza MD. The high-sensitivity C-reactive protein level one month after bare-metal coronary stenting may predict late adverse events. Rev Esp Cardiol. 2008 Mar;61(3):313-6.

110. Hernandez C, Francisco G, Ciudin A, Chacon P, Montoro B, Llaverias G et al. Effect of atorvastatin on lipoprotein (a) and interleukin-10: a randomized placebo-controlled trial. Diabetes Metab. 2011 Apr;37(2):124-30.

111. Fieseler HG, Armstrong VW, Wieland E, Thiery J, Schutz E, Walli AK et al. Serum Lp(a) concentrations are unaffected by treatment with the HMG-CoA reductase inhibitor Pravastatin: results of a 2-year investigation. Clin Chim Acta. 1991 Dec 31;204(1-3):291-300.

112. Klausen IC, Gerdes LU, Meinertz H, Hansen FA, Faergeman O. Apolipoprotein(a) polymorphism predicts the increase of Lp(a) by pravastatin in patients with familial hypercholesterolaemia treated with bile acid sequestration. Eur J Clin Invest. 1993 Apr;23(4):240-5.

113. Van Wissen S, Smilde TJ, Trip MD, de Boo T, Kastelein JJ, Stalenhoef AF. Long term statin treatment reduces lipoprotein(a) concentrations in heterozygous familial hypercholesterolaemia. Heart. 2003 Aug;89(8):893-6.

114. Gonbert S, Malinsky S, Sposito AC, Laouenan H, Doucet C, Chapman MJ et al. Atorvastatin lowers lipoprotein(a) but not apolipoprotein(a) fragment levels in hypercholesterolemic subjects at high cardiovascular risk. Atherosclerosis. 2002 Oct;164(2):305-11.

115. Goudevenos JA, Bairaktari ET, Chatzidimou KG, Milionis HJ, Mikhailidis DP, Elisaf MS. The effect of atorvastatin on serum lipids, lipoprotein(a) and plasma fibrinogen levels in primary dyslipidaemia--a pilot study involving serial sampling. Curr Med Res Opin. 2001;16(4):269-75.

116. Ozaki K, Kubo T, Imaki R, Shinagawa H, Fukaya H, Ohtaki K et al. The anti-atherosclerotic effects of lipid lowering with atorvastatin in patients with hypercholesterolemia. J Atheroscler Thromb. 2006 Aug;13(4):216-9.

117. Tsimikas S, Witztum JL, Miller ER, Sasiela WJ, Szarek M, Olsson AG et al. High-dose atorvastatin reduces total plasma levels of oxidized phospholipids and immune complexes present on apolipoprotein B-100 in patients with acute coronary syndromes in the MIRACL trial. Circulation. 2004 Sep 14;110(11):1406-12.

118. Krempler F, Kostner GM, Roscher A, Haslauer F, Bolzano K, Sandhofer F. Studies on the role of specific cell surface receptors in the removal of lipoprotein (a) in man. J Clin Invest. 1983 May;71(5):1431-41.

119. Kostner GM, Gavish D, Leopold B, Bolzano K, Weintraub MS, Breslow JL. HMG CoA reductase inhibitors lower LDL cholesterol without reducing Lp(a) levels.Circulation. 1989 Nov;80(5):1313-9

120. Hernandez C, Chacon P, Garcia-Pascual L, Simo R. Differential influence of LDL cholesterol and triglycerides on lipoprotein(a) concentrations in diabetic patients. Diabetes Care. 2001 Feb;24(2):350-5