1.1 The coronary arteries which encircle and nourish the heart are the common targets for damage caused by atherosclerosis thus resulting in coronary artery disease (CAD). Atherosclerosis causes narrowing of arterial lumen by fatty plaque which is characterised by lipid deposits. However, atherosclerosis can affect arteries virtually anywhere in the body. When it occurs in the neck or arterial circulation of brain; it can result in stroke. Arteries supplying the legs can get similarly affected like the coronary arteries thus resulting in peripheral arterial disease (PAD). Atherosclerosis of peripheral arteries can cause pain in calf muscles and in severe cases it can result in gangrene and amputation. The atherogenic lipids infiltrate a damaged area of the vessel wall and can cause thickening of vessel wall resulting in formation of a plaque. The lumen of the artery becomes narrowed which may be blocked completely by an atherosclerotic plaque thus resulting in Ischemia, a condition in which arterial blood flow is impeded as a result, little oxygen is delivered to the risk factors for PAD is identical to that of CAD. This includes smoking, hyperlipidaemia, hypertension, diabetes and obesity smoking in particular is important risk factor for peripheral artery disease. The classic symptom of PAD is crampy leg pain while walking, which is called as intermittent claudication. Pain may get worsened when a person walks faster or uphill. The pain usually subsides when he or she rests. The main cause of pain is ischemia in the working muscles, a sort of “leg angina.” (Angina pectoris or chest pain which is caused by inadequate blood supply to the heart muscle). Claudication pain is most often triggered by exercise. Other factors that can trigger the claudication pain include exposure to cold or certain medications, such as beta blockers which constrict blood vessels and decrease peripheral blood flow. The location and severity of the blockage determines the symptoms when the obstruction is relatively low in the arterial branches supplying the legs, claudication pain in calf muscles is the characteristic symptom. Higher block may result in thigh pain and blockage higher than the groin (in the blood vessels in the abdomen) may also result in buttock pain and impotence. When arteries are severely narrowed or blocked, leg pain may be noticed even at rest. At this point, the legs may appear normal whereas toes may appear pale,
discoloured, or bluish (especially when the legs are dangling) and feet will be cold to the touch. Pulses in the legs may be weak or absent. In the most advanced cases blood starved tissues may actually begin to die. Lower-leg, toe, or ankle ulcers may occur, and in the most advanced cases, gangrene may occur which may require amputation of toes or feet.¹

Global and National Scenario: Peripheral arterial disease (PAD) is associated with significant morbidity and mortality and is an important marker of subclinical coronary heart disease. However, it is estimated that PAD prevalence in the general US population has varied widely. The prevalence was 14.5%. In age- and gender-adjusted logistic regression analyses, black race/ethnicity, current smoking, diabetes, hypertension, hypercholesterolemia, and poor kidney function were positively associated with prevalent PAD. More than 95% of persons with PAD had one or more cardiovascular disease risk factors. Elevated fibrinogen and C-reactive protein levels were also associated with PAD. PAD affects more than 5 million adults. PAD prevalence increases dramatically with age and disproportionately affects blacks. The vast majority of individuals with PAD have one or more cardiovascular disease risk factors that should be targeted for therapy.²

The epidemiology of peripheral vascular disease has rarely been studied in non-European populations. The prevalence and risk factors of peripheral vascular disease (PVD) among South Indians was studied where subjects underwent an oral glucose tolerance test and were categorized as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or diabetes. Peripheral Doppler studies were performed on 50% of the study subjects, and PVD was defined as an ankle-brachial index (ABI) between 0.9 to 1.4, with abnormal ABI below 0.9 is an independent marker of cardiovascular risk. The prevalence rates of PVD were 2.7, 2.9, and 6.3% in individuals with NGT, IGT, and diabetes, respectively. The overall prevalence rate was 3.2%. Known diabetic subjects had a higher prevalence of PVD (7.8%) compared with newly diagnosed diabetic subjects (3.5%). PVD was uncommon until middle-age and then the prevalence rate increased dramatically. The prevalence of PVD in this urban South Indian population is considerably lower than that
reported in European and U.S. studies and is in marked contrast to the high prevalence rate of CAD reported in this population.\textsuperscript{3}

Since natural history of PAD indicates that among patients with intermittent claudication, 7\% will undergo lower extremity bypass surgery, which includes 4\% major amputations and 16\% worsening claudication. In non-fatal cardiovascular events such as MI, stroke occurs approximately 20\% over a 5 years period and 5 years mortality rate is estimated to be 30\% as compared to 10\% in controls, of which 75\% were cardiovascular deaths.\textsuperscript{4}

**Classification of PAD patient:**

1. **Asymptomatic PAD**
   Asymptomatic PAD is typically suspected by clinical examination of the lower extremity pedal pulses. The ABI is a simple test that can be conducted in the office and typically would confirm the presence of disease. An ABI is calculated by dividing the ankle pressure over the highest brachial pressure. An ABI \(<0.9\) is abnormal and indicates PAD. An ABI between 0.7 and 0.9 is considered mild disease, 0.5 and 0.69 is moderate disease, and less than 0.5 is severe disease.

2. **Intermittent claudication (IC)**
   IC is defined as discomfort in the calf muscles with exertion that resolves after a few minutes of rest. IC is present in 5\% of men and 2.5\% of women over the age of 60. In a study by the natural history of 257 patients with IC but no rest limb pain were followed for a mean of 6.5 years. Rest pain or gangrene of the worst affected leg was 7.5\% in the first year after referral. Thereafter the rate was 2.2\% a year.\textsuperscript{5}

**Amputation**

Amputation is infrequent in claudicants and occurs in 5.8\% of patients at a mean follow-up of 2.5 years. There are many classifications for claudication and limb ischemia but a most utilized one is the Rutherford-Baker (R-B) classification: R-B I indicates essentially asymptomatic patients or symptoms at very high level of activity, R-B II is symptoms at moderate level of activity, R-B III is symptoms at low level of activity, R-B IV is symptoms at rest, R-B V is ulceration, R-B VI is
ulceration with tissue necrosis. Claudicants are considered in the R-B I-III. Typically, endovascular or surgical interventions are reserved for IC Class III and higher. 6

Pathophysiology of PVD: This can be explained through chronic limb ischemia and acute limb ischemia.

Chronic limb ischemia (CLI) is pain in the lower extremity at rest or ulceration with and without tissue necrosis (R-B IV-VI). Aggressive treatment of CLI is needed, as progression to amputation is frequent. In patients with wound ulcers treated without revascularization, a high incidence of amputation has been reported particularly in patients with an ABI <0.5 reported on the natural history of limb ulceration in 142 patients with 169 limbs having ischemic limb ulcerations and not surgical candidates because of co-morbidities or lack of suitable targets for revascularization. All ulcers were treated with a protocol emphasizing pressure relief, debridement, infection control, and moist wound healing. The incidence of diabetes mellitus was 70.4% in limbs and chronic renal insufficiency was 27.8%. Limb loss was more prevalent in patients with ABI <0.5, with 28% and 34% experiencing limb loss at 6 and 12 months, respectively, compared with 10% and 15% of limbs in patients with an ABI >0.5 (p = 0.01). Of all limbs included, 23% required amputation at 12 months. Overall the primary amputation rate in CLI patients is 10%–40% with a mortality rate of 20% at 1 year, 40%–70% at 5 years, and 80%–95% at 10 years. 7

Acute limb ischemia (ALI)

ALI occurs within hours of presentation and is associated with rest limb pain and a pulseless, painful foot. The vessel is typically occluded with a thrombus that has occurred on top of mild to severe lesions. Collaterals are generally minimal or none. ALI occurs because of plaque rupture followed by in situ thrombosis or migration of a clot from a proximal location. The treatment of ALI is an emergency to save the limb.
Modifiable risk factors of PAD

Modifiable risk factors for PAD are not different from patients with coronary artery disease. Major risk factors include smoking, hyperlipidaemia, hypertension, diabetes, and the metabolic syndrome. PAD is also more prevalent in males and in the elderly.

Exact mechanism is atherosclerosis and artery spasm. Hence there is arterial insufficiency which is based on arterial stenosis thus resulting in complete occlusion of the artery. When imbalance between need of peripheral tissues and blood supply is produced resulting in ischemia of thrombotic origin occurs.

i. Diabetes

Diabetes is one of the strongest predictors for PAD and its associated complications including higher mortality and amputation; the latter is predicted by the presence of neuropathy, retinopathy, low ABI, and male gender. In a cross-sectional analysis of a 4153 Greek adults\(^8\) the odds ratio for vascular disease was 1.94 (95% CI 1.35–2.47) for patients with the metabolic syndrome, 3.04 (95% CI 1.98–4.11) for patients with the metabolic syndrome and diabetes, and 1.48 (95% CI 1.12–1.92) for patients with the metabolic syndrome but no diabetes. In this study, the presence of the metabolic syndrome and diabetes yielded a higher risk for PAD. A study reported on 733 diabetic patients who were followed for 7 years after undergoing podiatric, circulatory, and neurophysiological examinations. Amputated patients were then compared with patients with no amputations. Using multivariate analysis, vibration perception threshold, low ABI, history of retinopathy, visual handicap, and male sex were independently associated with lower extremity amputation. Patient education is of paramount importance to reduce amputations in the diabetics secondary to foot ulceration.\(^9\)

ii. Smoking

Smoking is also a powerful risk factor for PAD promoting endothelial dysfunction, and altering lipid metabolism and coagulation\(^10\). A study followed 1592 men and women aged 55–74 years selected at random from 11 general practices in Edinburgh, Scotland for 5 years. The incidences of
PAD and CAD were 5.1% and 11.1%, respectively. Cigarette smoking was a stronger risk factor for PAD than for CAD. Smoking was associated with an increase in coagulation and endothelial dysfunction markers. Current smoking of 25 or more cigarettes increased the odds ratio of PAD by 7.3 times (95% CI 4.2–12.8)\(^ {11}\). Furthermore current smokers seem to have a higher rate of procedural complications following percutaneous interventions. In one study a total of 131 patients with PAD were evaluated for in-hospital predictors of complications following percutaneous peripheral intervention (PPI). Forty-five patients (34.4%) had recent onset of claudication and 15 (11.5%) had ulceration. Thrombus was angiographically visualized in 16.7% of patients. The best model associated with emergent salvage revascularization included cigarette smoking within the past year, recent onset of claudication, and percutaneous transluminal angioplasty treatment below the knee. Smoking was a strong independent predictor of the risk for unplanned urgent revascularization of the lower extremities following initial successful treatment.\(^ {12}\)

iii. Dyslipidaemia

Dyslipidaemia is also significant risk factors for PAD. Familial hypercholesterolemia increases the prevalence of PAD from 5-fold to 10-fold compared with non-hypercholesterolemia subjects and its treatment with statins reduces the incidence of IC and increases walking duration. In a study the predictive value of 11 lipid and non-lipid biomarkers as risk factors for development of PAD was compared. Out of 14 916 initially healthy US male physicians, 40–84 years of age, 140 developed symptomatic PAD and were age- and smoking-matched to 140 men who remained free of vascular disease during an average 9-year follow-up. Multivariate analysis showed that the total cholesterol-HDL-C ratio (RR for those in the highest vs lowest quartile, 3.9; 95% CI 1.7–8.6) and CRP (RR for the highest vs lowest quartile, 2.8; 95% CI 1.3–5.9) were the strongest independent predictors for development of PAD. The addition of CRP to standard lipid screening significantly improved risk prediction models based on lipid screening alone (p < 0.001).\(^ {12}\)
iv. Obesity

Obesity is also a significant risk factor for atherosclerosis and PAD. In one study body fat was strongly associated with elevated inflammation markers including CRP and fibrinogen, which are predictors for active diffuse atherosclerotic disease. In a study the prevalence of the metabolic syndrome in patients with atherosclerotic vascular disease was determined in 1117 patients, mean age was 60 years. The prevalence of the metabolic syndrome in the study population was 46%. Similarly prevalence of metabolic syndrome was 58% in PAD patients, 41% in CHD patients, 43% in CVD patients, and 47% in abdominal aortic aneurysm patients. Also a study showed that the waist-to-hip ratio was independently associated with PAD. In a cross-sectional study of 708 men, aged 55–74, the relationships between total body fatness (assessed by body mass index (BMI)) and abdominal fat distribution (assessed by waist-to-hip ratio) was determined in patients with PAD (assessed by ABI). BMI did not correlate with PAD, whereas an increased waist-to-hip ratio over the median value doubled the prevalence of arterial disease. After controlling smoking, diabetes, hypertension, high-density lipoprotein cholesterol, and triglycerides, increased waist-to-hip ratio was independently associated with PAD (OR 1.68; 95% CI 1.05–2.70).

v. Hypertension

Lastly, hypertension is also positively associated with PAD as shown in the National Health and Nutrition Survey (NHANES) data. In this study, 2174 participants >40 years of age from the 1999–2000 National Health and Nutrition Examination Survey were included. PAD (ABI <0.9 in either leg) was prevalent in 4.3% of patients. Among those >70 years of age, the prevalence was 14.5%. Current smoking (OR 4.46, 95% CI 2.25–8.84), diabetes (OR 2.71, 95% CI 1.03–7.12), hypertension (OR 1.75, 95% CI 0.97–3.13), hypercholesterolemia (OR 1.68, 95% CI 1.09–2.57), and low kidney function (OR 2.00, 95% CI 1.08–3.70) were positively associated with prevalent PAD. PAD prevalence appears to disproportionately affect blacks (OR 2.83, 95% CI 1.48–5.42).
Management of patients with PAD:

**Medical therapies**

The focus of PAD treatment is:

1) to reduce symptoms and improve quality of life.

2) to reduce overall cardiovascular morbidity and mortality.

**Smoking cessation**

This is an important step to reduce symptoms of claudication and the overall burden of cardiovascular complications of atherosclerosis. In a recent study current smoking and pack-years of smoking correlate with the presence of PAD and smoking cessation for 20 years or more was associated with a higher mean ABI and lower prevalence of lower ABI (<0.9) than current smokers. Smoking cessation and exercise are considered the two most important treatments for PAD.

**Exercise**

Exercise has also been shown to improve symptoms of claudication and prolong pain-free walking time and distance and improve peak oxygen consumption. Exercise needs to be performed regularly with benefit becomes noticeable in few months. The exact mechanism by which exercise contributes to improvement in walking distance is unclear. Exercise, reduced resting plasma short-chain acylcarnitine (associated with functional impairment of PAD patients) by 26% that correlated with improvement in peak walking time ($r = -0.78$, p less than 0.05). In a randomized study, 19 patients with disabling claudication were randomized to exercise (supervised treadmill walking [1 hour/day, 3 days/week, for 12 weeks] with progressive increases in speed and grade as tolerated) and compared with a control group. Exercise subjects increased their peak walking time 123%, peak oxygen consumption 30%, and pain-free walking time 165% (all $p < 0.05$). Control subjects had no change in peak oxygen consumption, but after 12 weeks, peak walking time increased 20% ($p < 0.05$). Exercise is an important therapeutic recommendation to patients with PAD.
In a study, thirty-three English-language studies were identified, of which 21 met the inclusion criteria. Overall, following a program of exercise rehabilitation, the distance (mean±SD) to onset of claudication pain increased 179% from 125.9±57.3 m to 351.2±188.7 m (P<.001), and the distance to maximal claudication pain increased 122% from 325.8±148.1 m to 723.3±591.5 m (P<.001). The greatest improvement in pain distances occurred with the following exercise program: duration greater than 30 minutes per session, frequency of at least three sessions per week, walking used as the mode of exercise, use of near-maximal pain during training as claudication pain end point, and program length of greater than 6 months. However, the claudication pain end point, program length, and mode of exercise were the only independent predictors (P<.001) for improvement in distances.\textsuperscript{19}

The study concluded that optimal exercise program for improving claudication pain distances in patients with peripheral arterial disease uses intermittent walking to near-maximal pain during a program of at least 6 months. Such a program should be part of the standard medical care for patients with intermittent claudication.

**Cilostazol**

This pharmacological agent also has been shown to increase walking distance after 24 weeks of treatment by a mean 54% from baseline compared with placebo or pentoxifylline. In a double-blind, placebo-controlled, multicentre, randomized trial to evaluate the relative efficacy and safety of cilostazol and pentoxifylline, 698 patients were randomly assigned to blinded treatment with either cilostazol (100 mg orally twice a day), pentoxifylline (400 mg orally 3 times a day), or placebo. The primary endpoint was walking distance with constant-speed, variable-grade treadmill testing at baseline and at 4, 8, 12, 16, 20, and 24 weeks. The improvement with pentoxifylline was similar (p = 0.82) to that in the placebo group whereas cilostazol increased walking distance by 54% from baseline.\textsuperscript{20} Cilostazol has multiple pharmacologic actions including reduction in platelet aggregation, vasodilatation and improving lipid profile.\textsuperscript{21}
INTRODUCTION

Statins

Statins have also been shown to reduce claudication and increase walking distance by 24% at 6 months and 42% at 1 year compared with placebo. Statins are also essential to reduce cardiovascular events in patients with atherosclerotic disease irrespective of lipid levels. In a study high-dose (40 mg/day) short-term therapy with simvastatin in 43 patients with symptomatic PAD and a total cholesterol >220 mg/dL improved walking performance (mean 126 m improvement in distance; 95% CI 101–151 m; p < 0.001), ankle-brachial pressure indices (mean, 0.09; 95% CI 0.06–0.12; p < 0.01), and symptoms of claudication compared with a control group of 43 patients receiving placebo. Statins are important drugs to reduce cardiovascular events in patients with documented vascular disease and therefore a low threshold to use these drugs in patients with PAD is warranted.22

Antithrombotic therapy (aspirin or ADP-receptor antagonists clopidogrel or ticlopidine)

Antithrombotic therapy has not been shown to improve symptoms of claudication but is important to reduce cardiovascular complications associated with the presence of atherosclerosis and PAD. The Antithrombotic Trialist Collaboration (2002) showed that a low dose aspirin (75–150 mg) reduces vascular events by 32% in the high-risk patient including the subset of patients with PAD (p = 0.004). In this meta-analysis of 287 randomized trials involving 135 000 patients in comparisons of antiplatelet therapy versus control and 77 000 in comparisons of different antiplatelet regimens among each others in high risk patients (with acute or previous vascular disease or some other predisposing condition), “serious vascular event” including non-fatal MI, non-fatal stroke, or vascular death were reduced in the antiplatelet group. In addition, in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial the long-term administration of clopidogrel to patients with atherosclerotic vascular disease (follow-up for 1–3 years) was more effective than aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death (5.83% versus 5.32% for aspirin versus clopidogrel respectively, p = 0.045).23
Ticlopidine also has protective effects probably similar to clopidogrel in the high-risk vascular patient but its adverse side-effects have limited its use. The CHARISMA trial has enrolled 15603 patients with established CAD, CVD, or PAD, or at high risk of developing atherothrombosis due to multiple risk factors. These patients were randomized to receive either clopidogrel or placebo, in addition to low- to moderate-dose aspirin. The rate of the primary efficacy end point was 6.8% with clopidogrel plus aspirin and 7.3% with placebo plus aspirin (RR 0.93; 95% CI 0.83–1.05; p = 0.22). Clopidogrel added to aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes. In the subgroup of patients with documented vascular disease, the rate was 6.9% with clopidogrel and 7.9% with placebo (RR 0.88; 95% CI 0.77–0.998; p = 0.046). There was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherosclerotic vascular disease and a suggestion of harm in patients with multiple risk factors but no documented atherosclerosis. Currently clopidogrel alone or aspirin alone are strongly recommended in patients with PAD. Patients, however, with a recent acute coronary syndrome will benefit from the combination of aspirin and clopidogrel for at least 1 year after the event.

Revascularization therapies

Revascularization is indicated for the relief of ischemic symptoms, particularly when medical therapy fails or is insufficient. There are two primary goals of revascularization: first, to relieve symptom-limiting claudication or rest ischemic pain; second, to minimize tissue loss or limit the degree of amputation.

Over the past decade, there has been an exponential rise in lower extremity PPI with a concomitant drop in surgical interventions. Most patients with advanced PAD have occult or symptomatic coronary/cerebral vascular disease, and thus the mortality of peripheral bypass surgery may exceed 10% in high-risk patients.

Minimally invasive endovascular therapy offers inherent advantages over traditional surgical revascularization, such as lower morbidity, shorter hospital length of stay, and considerably less
patient discomfort. As the field of endovascular therapy continues to grow, the need for traditional surgical therapies will be considerably reduced.

In summary, PAD is a part of a diffuse atherosclerotic problem and a marker of cardiac and cerebrovascular mortality. Initial therapy is preventive for all patients with a focus on aggressively controlling modifiable traditional risk factors for coronary artery disease and PAD. Smoking cessation, controlling elevated blood pressure and blood glucose, losing excess body fat, exercise, treating hyperlipidaemia with statins, and the use of antiplatelet are crucial first steps in the management of the PAD patient. Revascularization is reserved for the very symptomatic patient or those with critical limb ischemia.

1.2 Definition of the Problem: In India there are few studies with respect to stages of the disease requiring surgical intervention. Similarly there are few studies, highlighting the effectiveness of physical training and rehabilitation in different stages of the arterial occlusive disease having Ischaemic neurological damage. Thus, there is a dilemma in the mind of the physician, surgeon and physiotherapist to decide whether to use conservative management alone such as medication, rehabilitation programme or surgical management alone or combination of medical and surgical managements for patients with Ischaemic neuropathy after acute or chronic arterial disease. So, it has been proposed here to test predictive criteria for selection of patients for physiotherapy and rehabilitation in patient with Ischaemic neurological damage.

1.3 Bases of Hypothesis: Based on research problem/need for study hypothesis of the study has been framed.