

Profile of Atherosclerotic Risk Factors and Management in Patients of Peripheral Arterial Disease at a Tertiary Care Teaching Hospital of North India

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Peripheral arterial disease, being a manifestation of systemic atherosclerosis, carries a high risk of adverse cardiovascular events. Secondary medical prevention therapies of same magnitude as that for coronary artery disease are recommended for peripheral arterial disease patients also. Available evidence indicates that this condition commonly remains underdiagnosed and undertreated. There is lack of any report about management of these patients in India. The objectives of the present study were to characterize the atherosclerotic risk factor profile and pattern of drug prescription for patients of peripheral arterial disease at a tertiary care teaching hospital and to compare this management with standard guidelines. Data were collected from prescriptions of patients attending cardiothoracic and vascular surgery outpatient department with diagnosis of atherosclerotic peripheral arterial disease from July 2012 to Jun 2013. One hundred twenty prescriptions were analysed. The mean age (\pm SD) of patients was 53 ± 7.18 years and 23.3% were females. History of smoking, either past or present, was present in 91.6% patients. History of ischemic heart disease was present in 25%, while 26.7% patients were diabetic. Mean number of cardiovascular risk factors was 2.6. The percentage of eligible patients who were receiving a particular drug was 100% for aspirin and statins, 48.3% for angiotensin converting enzyme inhibitors, 46.7% for beta blockers and 66.7% for cilostazol. The vascular surgeons of this centre are using antiplatelet agents and statins adequately for peripheral arterial disease. The prescription of angiotensin converting enzyme inhibitors, beta blockers and cilostazol is low. Exercise therapy and smoking cessation need more attention.

Key words: Cardiovascular disease, atherosclerosis, peripheral arterial disease, smoking cessation

Peripheral arterial disease (PAD) is a common disorder which affects large populations of adults worldwide. It most commonly affects arteries of the lower limb and patients mostly present with intermittent claudication. Atherosclerosis is the leading cause of PAD. The prevalence of PAD differs depending upon diagnostic criteria as well as age and risk factors profile of the study population and may range from 3-12%^[1]. Prevalence increases further with advancing age and may reach 15-20% in persons >65 years^[2,3]. Recently, it was estimated that 54.8 million people were living with PAD in southeast Asia in 2010 (out of 202 million globally)^[4].

Due to the common underlying pathologic process (i.e. atherosclerosis), PAD is commonly coexistent

with coronary artery disease (CAD) and/or cerebrovascular disease (CVD), which may be diagnosed or undiagnosed. PAD is said to be the third leading cause of atherosclerotic cardiovascular morbidity, following CAD and stroke^[4]. Patients of PAD have a 6.6 fold increased risk of death from CAD^[5]. Due to this high risk, PAD is considered to be a CAD equivalent condition and requires intensive risk reduction therapy. There is evidence that a large proportion of PAD patients are not treated with atherosclerotic risk reduction therapies (e.g. antiplatelet drugs, statins, angiotensin converting enzyme (ACE) inhibitors)^[6-8] despite of evidence that these therapies improve survival in these patients^[9,10]. The present study was done to assess the patterns of atherosclerotic risk factors and their management in lower extremity PAD patients at a tertiary teaching hospital of north India.

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MATERIALS AND METHODS

Data acquisition:

Data were collected prospectively from prescriptions of patients attending cardiothoracic and vascular surgery OPD with diagnosis of atherosclerotic PAD from July 2012 to Jun 2013. Ethical clearance was obtained from Institutional Ethics Committee of the hospital.

Pattern of risk factors:

All prescriptions were analysed for presence of risk factors for atherosclerosis (history of smoking, hypertension, diabetes, dyslipidemia, renal insufficiency, history of ischemic heart disease or cerebrovascular disease), smoking cessation efforts and advice regarding exercise. Ankle brachial index (ABI) was documented if present on prescription.

Pattern of drug prescription:

Prescription of drugs for modification of atherosclerotic risk factors (aspirin, ACE inhibitors, beta blockers and lipid lowering drugs) and for intermittent claudication (cilostazol and pentoxifylline) was recorded. Prescription of drugs for other purposes (e.g. antacids, analgesics or antipyretics, multivitamins) was not recorded.

Assessment of eligibility for drugs:

Each prescription was analysed for eligibility for drugs for modification of atherosclerotic risk factors (aspirin, ACE inhibitors, beta blockers and lipid lowering drugs) and for drugs for intermittent claudication (cilostazol and pentoxifylline). Eligibility was decided based on ACC/AHA and TASC-II guidelines for management of patients of PAD^[11,12]. All patients were considered to be eligible for aspirin, ACE inhibitors, lipid lowering drugs and cilostazol. In addition, patients with history of ischemic heart disease (IHD) were considered as eligible for beta blockers. Patients were considered eligible for pentoxifylline only if cilostazol was contraindicated/not tolerated.

RESULTS AND DISCUSSION

A total of 120 prescriptions were analysed. Basal patient characteristics and risk factors for atherosclerosis are presented in Table 1. The mean number of cardiovascular risk factors (smoking, diabetes, hypertension, dyslipidemia) was 2.6, where

29% patients had all 4 risk factors, 35.5% had any 3 risk factors and 65% had any two risk factors.

A record of ABI was present on 74 (61.1%) prescriptions. Based on ABI value, mild to moderate PAD (ABI 0.41-0.90) was present in 66 patients while 8 patients had severe PAD (ABI \leq 0.40). Advice to quit smoking was offered to all current smokers. Nicotine replacement therapy (patch or gum) was advised to 5 patients. All patients were advised regular walking.

Fig. 1 shows the prescription pattern of drugs for modification of atherosclerotic risk factors (aspirin, statins, ACE inhibitor, beta blocker) or for the treatment of intermittent claudication (cilostazol). All patients were prescribed aspirin. Statin was prescribed to 86 patients while ACE inhibitor (ramipril)

TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS

Characteristics	Mean \pm SD/number (percent)
Age (years \pm SD)	53 \pm 7.18
Males	92 (76.6)
Females	28 (23.3)
Current smokers	76 (63.3)
Past smokers	34 (28.3)
Diabetes	32 (26.6)
Hypertension (BP >140/90 mm Hg nondiabetics, >130/80 mm Hg diabetics)	85 (71.6)
Abnormal lipid profile (LDL >100 mg/dl)	86 (71.6)
Renal insufficiency	7 (5.8)
History of IHD	30 (25)
Angina	22
MI	8
Angioplasty/CABG	6
History of TIA/CVA	6 (5)

LDL is low density lipoprotein, IHD is ischemic heart disease, MI is myocardial infarction, CABG is coronary artery bypass grafting, TIA is transient ischemic attack, CVA is cerebrovascular accident (N=120)

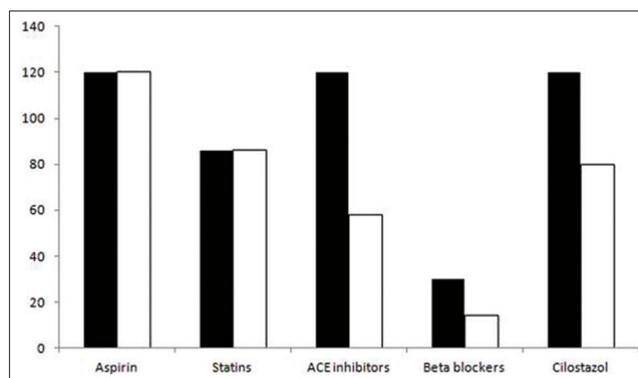


Fig. 1: Pattern of drug prescription for PAD patients.
 ■ Eligible patients □ Patients receiving treatment.

was prescribed to 58 patients. Pentoxifylline was prescribed to 72 and cilostazol to 80 patients. Beta blocker was prescribed to 14 patients.

PAD is said to be a global problem of 21st century affecting low and middle income countries worse than high income countries^[4]. Evidence exists that there is a lack of awareness of PAD and these patients are usually under diagnosed and under treated^[3,6,8,13]. To our knowledge, there is no study reporting pattern of drugs which are being used in India for management of PAD. Therefore, the present study is first to describe pattern of atherosclerosis risk factors and their management in Indian patients of PAD.

ABI is a simple and noninvasive test for establishing a diagnosis of PAD. ABI is the ratio of systolic blood pressure at ankle to that at arm. In normal individuals, ankle systolic pressure is 10-15 mm Hg higher than brachial systolic pressure and thus the normal ABI value is more than 1.00. A value of $ABI \leq 0.90$ is diagnostic of PAD with values between 0.41 and 0.90 reflect mild to moderate PAD and values ≤ 0.40 reflect severe PAD^[11]. In the present study ABI value was available in only 61.1% prescriptions, however in others it was not taken either because of lack of time or because of unawareness of its relevance. ABI has prognostic value not only in predicting wound healing and limb survival but also as an independent predictor of mortality in PAD patients^[14]. It becomes even more important in those patients in whom surgical revascularisation planned. Low ABI values have been correlated with high risk of both cardiovascular and cerebrovascular events^[15]. Thus, abnormal ABI can serve as a surrogate marker for systemic atherosclerosis.

In the present study, out of 120 patients, history of either current or past smoking was documented in 110 (91.6%) patients. Smoking is a well known risk factor for PAD and appears to be more strongly related with PAD than with CAD^[16]. The odds of developing PAD may be as high as 2.3 for former smokers and 4.3 for current smokers. Although evidence also exists for dose response relationship between pack years of smoking and PAD, the number of cigarettes or duration of smoking was not documented in the present study. Smoking may contribute to atherosclerosis, by causing endothelial dysfunction, abnormal lipid profile and altered platelet function.

In the present study, all patients who were smokers were advised to stop smoking; only 5 patients were prescribed nicotine replacement therapy (NRT) in the form of gum (3 patients) and patch (2 patients). Although effective, physician's advice alone has a low rate of cessation^[17]. ACC/AHA guidelines recommend use of any one of the three pharmacotherapies for smoking cessation i.e. nicotine replacement therapy (NRT), bupropion and varenicline. Although the hazards of smoking are well known to medical community, the under use of smoking cessation interventions by medical professionals has been reported^[18-20]. Thus, there is an urgent need to enhance training of medical professionals in effective utilisation of smoking cessation interventions. This training should preferably start right from undergraduate period and may be taught to medical students along with subjects of pharmacology, community medicine or general medicine.

All patients in the present study were advised regular walking but there was no specific advice regarding this. Supervised exercise training (SET) programme has been shown to benefit PAD patients, as it increases maximal walking distance by upto 200%^[21]. Supervised exercise training is a class I recommendation by ACC/AHA guidelines and should be performed for a minimum of 30 to 45 min in sessions performed at least 3 times per week for a minimum of 12 weeks. In addition, regular exercise programme may be expected to decrease cardiovascular risk in this high risk population. Thus, SET is the only intervention which provides improvements in symptoms and reduces cardiovascular risk both. Despite of these favourable effects, the usefulness of SET remains limited due to the problems of accessibility, travel time and cost. Home based exercise programme is a viable alternative to SET programme when SET is not available or unaffordable. Although less effective than SET, home based exercise programmes can improve walking capacity and quality of life when compared to usual care^[22]. Moreover, home based programmes are reported to have higher adherence rates in the long term^[23].

History of type 2 diabetes was present in 32 (26.6%) patients. PAD is one of the macrovascular complications of type 2 diabetes and every 1% increase of hemoglobin A1C increases the risk of PAD by 28%^[24]. The high prevalence of PAD among

diabetic population further emphasizes the importance of measurement of ABI in all diabetics. Ischemic heart disease was present in 30 (25%) patients. Contrary to popular belief, beta blockers are not contraindicated in PAD patients^[11] rather they have been shown to decrease incidence of new coronary events by 53% in PAD patients with prior myocardial infarction^[25]. Due to their basal cardioprotective effect, beta blockers should be used in all PAD patients who have ischemic heart disease.

Antiplatelet therapy has been shown to reduce adverse cardiovascular events including MI, stroke or vascular death among patients of PAD^[26]. Also, low dose aspirin has been shown to reduce the need for peripheral arterial surgery^[27]. In the present study all the patients were prescribed aspirin (75-100 mg). The benefits of lowering serum LDL-C with statins in patients of PAD have been reported previously^[28]. In addition to prevention of adverse cardiac events, statins have been shown to benefit symptom of intermittent claudication also^[29,30]. In the present study, statins (most commonly atorvastatin 20-40 mg) were prescribed to all patients (n=86) who had high LDL (>100 mg/dl). This reflects improved prescription of statins when compared to previous reports about lower statin use by vascular surgeons^[31,32]. This improvement in statin use may be due to frequent CME programmes at our hospital which provide opportunity for communication with other specialists e.g. cardiologists. According to ACC/AHA guidelines, LDL goal of <70 mg/dL should be achieved in those PAD patients with very high risk of ischemic events (e.g. diabetes or continued smoking or low HDL cholesterol). If the maximum dose of a single statin fails to achieve this goal then a fibric acid derivative may be combined.

ACE inhibitors are another group of drugs which benefit PAD patients. These agents have been shown to increase resting blood flow as well as blood flow after exercise; they also increase pain free and maximum walking times with improvement in quality of life^[33]. In the HOPE study, ramipril was found to reduce major cardiovascular events in both symptomatic as well as asymptomatic PAD^[34]. These vasculoprotective effects of ACE-I appear to be independent of their antihypertensive property and may be due to improvement in endothelial function and decreased accumulation of macrophages in intima of arteries, one of the initial steps in the pathogenesis

of atherosclerosis. In addition, they also improve insulin resistance and reduce the incidence of type 2 diabetes^[35], which is a predisposing factor for PAD. Based on these findings, ACE inhibitor therapy has been suggested as the routine treatment of PAD, regardless of presence or absence of hypertension^[36]. In the present study, ACE inhibitors were prescribed to 58 patients only. This underuse of ACE inhibitors in PAD patients has been reported previously also^[10,13,37,38].

Cilostazol is a phosphodiesterase 3 inhibitor having antiplatelet and vasodilator properties. It has been shown to improve maximal walking distance by upto 60% after 12-24 weeks of treatment^[39]. Apart from these effects, cilostazol has been shown to increase HDL cholesterol and decrease plasma triglyceride levels^[40]. However, the clinical relevance of these positive changes in lipid profile remains unknown. It is recommended for all patients of intermittent claudication in the absence of heart failure. While all 120 patients in the present study were eligible for cilostazol, it was prescribed to 80 patients only. Headache, diarrhea and palpitations are common side effects of cilostazol, which may be responsible for underuse of this drug.

Pentoxifylline increases blood flow to the microcirculation and improves oxygenation by reducing blood viscosity and increasing erythrocytic flexibility. The efficacy of pentoxifylline in PAD has been shown to be inferior to that of cilostazol and in one study, was not significantly different from placebo^[41]. It is recommended for those patients of intermittent claudication who do not tolerate cilostazol or have contraindication for it. In the present study, 72 patients were prescribed pentoxifylline. The reasons for popularity of pentoxifylline seem to be that it was the first drug approved for intermittent claudication and also has better tolerability than cilostazol. One of the reasons for this ambiguity is absence of any national guidelines for management of PAD in India.

PAD is a manifestation of systemic atherosclerosis and patients are at high risk of adverse cardiovascular events. These patients need aggressive risk factor reduction similar to patients of CAD. Medical therapy can substantially improve survival in this group of patients. The utilisation of smoking cessation interventions can help smokers stop smoking and

thus reduce the cardiovascular risk. Regular exercise should be promoted by both supervised as well as home based programmes. While antiplatelet agents and statins are being used adequately; use of ACE inhibitors, beta blockers and cilostazol is suboptimal and needs to be increased. Awareness of recognition and optimum management of PAD has to be improved not only among vascular surgeons but all the medical and surgical specialities.

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