

## Prevalence of Asymptomatic Carotid Artery Stenosis (ACAS) in patients with peripheral artery disease (PAD)

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### Introduction

Atherosclerosis , being a systemic disease ,affects coronary arteries , peripheral vasculature as well as cerebral vasculature, sometimes simultaneously.

Risk factors for atherosclerosis include increasing age, smoking, diabetes and hypertension. While concomitant involvement of different vascular beds is not so uncommon, such incidence portends poorer prognosis<sup>1</sup>. Multiple studies have reported that the prevalence of asymptomatic carotid artery stenosis is quite high in patients with peripheral arterial disease<sup>2-5</sup>; The prevalence and severity of carotid artery stenosis have been shown to significantly increase

in subjects with PAD regardless of the clinical symptoms<sup>6</sup>. Crude incidence of stroke ranged from 108 to 172/100,000 people per year, crude prevalence from 26 to 757/100,000 people per year and one-month case fatality rates from 18% to 42%. Incidence of ischemic stroke amounts to about 74% of all stroke cases<sup>7</sup>. To prevent ischemic stroke carotid endarterectomy has been recommended in patients with significant extracranial carotid artery stenosis. Asymptomatic Carotid Atherosclerosis Study (ACAS) demonstrated the benefit of performing carotid endarterectomy in selected asymptomatic patients with significant carotid artery stenoses (60% stenosis)<sup>7</sup>.

Carotid duplex ultrasonogram is an accuracy proven non-invasive diagnostic examination to detect carotid artery stenosis. Routine carotid artery screening is not recommended due to relative overall incidence of carotid artery disease.

Since the increased incidence of ACAS was well documented in patients with PAD, carotid ultrasonogram screening is helpful in these populations.

The goal of this study was to 1) Evaluate the association between PAD and asymptomatic carotid artery stenosis (ACAS), a well-defined asymptomatic measure of cerebrovascular disease; and 2) to identify the specific at “risk population” among the PAD patients who benefit from routine carotid duplex screening.

### Materials and methods

The study population includes patients presented with complaints of limb ischemia to Govt Rajaji Hospital and, Madurai . 147 PAD patients who were admitted for limb revascularisation in the index hospital between April 2021 and April 2022 were included in the study based on the inclusion and exclusion criteria. Patients who Subjects with any history of neurological symptoms, previous stroke, or previous carotid endarterectomy were excluded . Similarly , patients who underwent emergency procedures of limb revascularisation were excluded . Out patient patients and claudicants who were managed conservatively on outpatient basis were also excluded from the study considering the difficulty in follow up. PAD was defined as ABI less than 0.90 or more than 1.3<sup>9</sup>. ABI for a limb is measured by dividing the higher of ankle pressures(among dorsalis pedis and posterior tibial artery) of the index limb with higher of the systolic brachial pressures.

Severity based on ABI is defined as

>1.30	Non compressible
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0.9 – 1.3	Normal
0.7 - 0.89	Mild PAD
0.4 – 0.69	Moderate PAD
< 0.4	Severe PAD

CT/MR angiogram was done to evaluate the distribution of lesion. The lesion distribution was further categorised into Infra-inguinal(involving femoral and tibial vessels), Supra-inguinal(which include iliac arteries and infrarenal abdominal aorta) and multiple/multilevel occlusion. A total of 232 patients underwent limb revascularisation during this period, of which patients who underwent emergency procedures or previous carotid endarterectomy and the PAD patients with non-atherosclerotic etiology were excluded from the study. Clinical characteristics such as age , gender ,diabetes mellitus , smoking history, CAD ,CKD, ankle brachial index (ABI) – to assess the severity of limb ischemia , distribution of lesion are matched and reviewed during analysis. High resolution B-mode ultrasonography , Hitachi EUB.525 ultrasound machine (Hitachi Medical Corp, Tokyo, Japan), with a 7.5 MHz linear-array transducer was used evaluate the carotid vessels to evaluate the presence and site of plaques and to qualify the degree of stenosis . All scans were done by single radiologist with 15 years of experience in vascular ultrasonography. Severity of carotid disease was defined based on guidelines by Society of radiologists in ultrasound consensus conference<sup>10</sup>. Patients were divided into the following 4 groups.

- 1) Less than 50% stenosis,
- 2) 50% – 69% stenosis,
- 3) >70 % stenosis and
- 4) The unstable plaque

Unstable or vulnerable plaque was defined as per ultrasonographic characteristics - A thin cap with a large lipid core . These plaques have a cap thickness of <100  $\mu$ m and a lipid core accounting for >40% of the plaque's total volume. The term ‘vulnerable’ plaque was coined by Muller and colleagues, to describe a plaque that by becoming disrupted has a high likelihood of starting the adverse cascade<sup>11</sup>

Statistics : The data were presented as mean  $\pm$  standard deviation or percentage. Statistical analysis was performed using Chi square test and Fisher’s exact test ,whenever appropriate.  $p$  value < 0.05 was considered statistically significant.

## **Results**

Among the 147 patients included in the study, the mean age was  $56 \pm 10$  years , ranging from 51 years to 73 years . 87% patients (127/147) were male. 14% (20/147) patients had infra-inguinal disease and 49% (72/147) patients had multiple lesions.

<b>CHARACTERISTICS</b>	<b>N = 147</b>
Mean Age , years	$56 \pm 9.72$
Gender , Male	127(87%)
Smoking	116(78%)
Hypertension	91(62%)

Diabetes mellitus	69(47%)
Coronary artery disease (CAD)	10(7%)
Chronic kidney disease (CKD)	4(3%)
Old Cerebrovascular disease (CVD)	3(2%)
Hyperlipidemia	9(6%)

Prevalence of ACAS based on PAD was found to be as stated below

109(74.14%) patients had < 50% stenosis ,16(10.80%)patients had between 50%- 69% stenosis

17(11.56%)patients had >70% stenosis and 5(3.40%) patients were found to have an unstable plaque

Patients with unstable plaque underwent carotid endarterectomy before limb revascularisation while the rest of the patients were managed appropriately after limb revascularisation.

Prevalence of ACAS based on anatomical site of the peripheral arterial disease –

	Suprainguinal	Infrainguinal	Multiple
< 50%	18(90%)	45(81.8%)	46(63%)
50% – 69%	1(5)	5(9%)	10(13.8%)
>70%	1(5%)	5(9%)	11(15.2%)
Unstable plaque	0	0	5(6.9%)

Combined lesions involving supra and infra-inguinal regions presented higher incidence of severe ICA stenosis ( $p = 0.016$ ). Based on severity of PAD (by the measure of ABI), the distribution of ACAS patients was as follows

ABI*	50%– 69%	>70%	Unstable plaque
0.7–0.89	2( $p = 0.31$ )	2( $p = 0.33$ )	0
0.5–0.69	6( $p = 0.18$ )	4( $p = 0.21$ )	0
0.4–0.49	8( $p = 0.06$ )	4( $p = 0.21$ )	1
< 0.4	0	7( $p = 0.04$ )	4( $p = 0.03$ )

\*in patients with both lower limb involvement, lower ABI among both limbs was considered

ABI < 0.4 ,which signifies severe form of PAD is significantly associated with ACAS ,which implies positive correlation between severity of PAD and ACAS as well as the severity of carotid stenosis.

Analysis of individual risk factors for severity of ICA stenosis in PAD patients

On a multivariate analysis the following risk factors were found to have significant association with severity of carotid artery stenosis

	Confidence index	Odds ratio	<i>P</i> value
<b>Age &gt; 63</b>	1.02 – 1.14	1.061	<b>0.031</b>
Diabetes Mellitus	0.55 – 3.10	1.360	0.339
Hypertension	0.24 – 1.30	0.530	0.421
Smoking	0.31 – 2.21	0.860	0.752
<b>CKD</b>	1.13 – 16.42	9.370	<b>0.0129</b>
CAD	0.23- 10.11	1.540	0.352
<b>H/O Stroke</b>	1.08-15.89	3.972	<b>0.036</b>

Age > 63 years , Old CVD , CKD and ABI < 0.4 Were found to have significant association with the severity of CAS.

### **Discussion**

The strong association of Carotid artery disease with PAD was well known. The prevalence and severity of carotid artery stenosis have been shown to significantly increase in subjects with PAD regardless of clinical symptoms<sup>12</sup> . Perioperative and post operative stroke remains one of the major complications of peripheral artery vascular surgery causing significant morbidity and mortality<sup>13</sup> . CUS screening of asymptomatic patients for more than 70% stenosis and timely intervention can increase quality adjusted life years and also can be cost effective<sup>14</sup> . The prevalence of ACAS is much higher in patients with PAD compared to the general population, the association of PAD with prevalence and severity of carotid artery stenosis was studied. Though the prevalence of ACAS in symptomatic PAD population was studied before, attempt was made to identify the subset of patients among the PAD patients who are at greater risk of harbouring ACAS . The univariate and multivariate risk analysis of associated risk factors was done in conjunction, to stratify high risk groups among the PAD patients who require pre-op CUS screening. While the prevalence of ACAS among PAD patients included in this study stood at 17% , about 3% patients had an unstable plaque ,which ,as mentioned earlier ,is a significant marker of future stroke.

The patients with unstable plaque promptly underwent carotid endarterectomy ,thus proven to be benefited from the carotid screening .However, the patients with >70% carotid artery stenosis opted out of intervention on carotid vessels after risk benefits of both medical management and carotid intervention were explained (CEA and CAS were both included among the interventional treatment options offered) . Such patients were initiated on best medical therapy and are on regular follow up.

A meta-analysis of 19 studies showed high prevalence of asymptomatic carotid artery stenosis exists in patients with PAD<sup>15</sup> . A prevalence of >70% ACAS was 14% and the authors suggested targeting PAD patients rather than a healthy population if

routine screening is performed. A study conducted by *Woo-Sung Yun, Young-Nam Rho,*

*Ui-Jun Park et al* in Korean population<sup>16</sup> estimated that the prevalence of ACAS in PAD was about 13.8%, closely corresponding to the meta-analyses. In our study, the prevalence clocked at 17% , a little higher than the above mentioned studies.

The patients were further stratified based on the level of occlusion and the patients with multilevel occlusion were found to have significant association with ACAS compared to isolated supra-inguinal or infra inguinal level occlusion.

Also the patients were stratified based on the severity of PAD , as dictated by the ABI . The positive association of ACAS with lower ABI (More severe forms of PAD) been found.

Regarding the risk factors of ACAS, previous studies reported that carotid bruit, rest pain, age > 65 years , and ABI < 0.7 were associated with > 50% stenosis of ICA<sup>17,18</sup>.

The association of independent risk factors of atherosclerosis and systemic conditions with ACAS was studied by *Woo-Sung Yun, Young-Nam Rho,Ui-Jun Park et al* in their study<sup>16</sup>.According to that study increasing age (>65years) and CAD were found to have an association with ACAS where as in our study age >63yrs , ABI < 0.4 , history of stroke(CVD) , CKD , multilevel peripheral arterial occlusion were significant risk factors for ACAS in PAD patients. However DM, CAD , HTN and smoking were not significantly associated with ACAS in PAD patients in this study.

Based on this study, the above mentioned high risk groups can be considered for routine carotid duplex screening ultrasonography

Limitations of the study include - (1) Operator dependency of the primary screening investigation (CUS) and Interpretation by single radiologist (2) Single centre and relatively short period of study (3) Exclusion of patients who were managed conservatively on outpatient basis (claudicants and patients not willing for intervention)

### **Conclusion**

Patients with ACAS accounted for about 38 patients among the studied PAD population (n = 147). 11 patients with severe stenosis and 5 patients with unstable plaque. The prevalence is found to be higher than in age ,sex matched normal population. Significant association of carotid artery stenosis was found in PAD patients with age > 63 years, History of stroke(CVD) , ABI < 0.4 and CKD patients. Pre-op screening with CUS for identifying this high risk group of patients for ACAS and timely intervention can significantly improve quality of life by prevention of intra-op and post op cerebrovascular adverse events . Availability of non-invasive screening modality (CUS) as well as the cost effectiveness and universal availability calls for inclusion of carotid screening as a routine protocol in the above mentioned high risk groups.

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**19 Co-existence of vascular disease in different arterial beds: Peripheral artery disease and carotid artery stenosis – Data from Life Line Screening®**

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