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# INTRODUCTION

Carotid artery disease is associated with a risk of stroke. Approximately 88% of strokes are ischemic and about 20% of these originate from large artery stenosis. To prevent ischemic stroke, carotid endarterectomy has been recommended for asymptomatic patients with severe carotid stenosis based on evidence from multicenter prospective randomized trials.

Carotid duplex ultrasonography (CDUS) is an accuracy-proven non-invasive diagnostic examination to detect asymptomatic carotid artery stenosis (ACAS). However, for the general population, CDUS has a limited role in screening of carotid disease because of a low overall prevalence of clinically relevant disease. Because coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral arterial disease (PAD) originate from atherosclerosis, these three diseases occasionally exist together. Therefore, screening CDUS may be useful for those populations. Several previous studies reported that the prevalence of ACAS was relatively high in patients with critical limb ischemia.

In India, the prevalence of asymptomatic carotid artery disease in patients with critical limb ischemia has not yet been reported.

Therefore, the aim of the present study was to determine the prevalence of asymptomatic carotid artery disease in a group of Indian patients with critical limb ischemia.

## AIM

- To study the prevalence of ASYMPTOMATIC CAROTID ARTERY DISEASE in patients with Critical Limb Ischemia.
- To identify predictive factors of ACAD in patients with CLI.

## MATERIALS AND METHODS

- 250 consecutive patients with critical limb ischemia admitted in our department underwent carotid duplex scanning.
- A questionnaire was used to collect data concerning known risk factors.

## INCLUSION CRITERIA

- Patients with critical limb ischemia.
- Age >30 yrs.

## EXCLUSION CRITERIA

- Known CVA patients.
- Patients with history of TIA.
- Previous carotid artery intervention.

## METHOD

- For all patients Carotid duplex scan was done by the Radiology department.
- Carotid lesions were documented using Modified Washington duplex criteria.

Modified Washington duplex criteria

| Stenosis | PSV | EDV | Spectrum |
|---|---|---|---|
| Normal | <125 cm/s | | Normal with no plaque |
| 1-15% (B) | <125 cm/s | | Normal with plaque |
| 16-49% (C) | <125 cm/s | | Broadening |
| 50-79% (D) | >125 cm/s | <140 cm/s | Broadening |
| 80-99% (D+) | >125 cm/s | >140 cm/s | Broadening |
| Occluded (E) | No flow | No flow | No flow |

PSV, peak systolic velocity; EDV, end diastolic velocity; cm/s, centimetres per second; CCA, common carotid artery; ICA, internal carotid artery; ECA, external carotid artery.

EDV: 80cm/s ~ 60%; 100 cm/s ~ 70%

ICA:CCA PSV ratio: 3.2 ~ 60%; 4.0 ~ 70%

## REVIEW OF LITERATURE

Worldwide stroke is the second leading cause of death, estimated to occur in just over 5 million people per year. Approximately two-thirds of cerebrovascular accidents are due to thromboembolic events, and extracranial atherosclerosis is the major contributor. The anatomic distribution of cerebrovascular atherosclerosis has been studied, and the breakdown by location in those with disease is as follows:

Carotid bifurcation 38%

Intracranial 33%

Arch-branch based 9%

Proximal vertebral 20%.

By far the most common lesion found in patients with extracranial cerebrovascular disease is an atherosclerotic plaque in the carotid bifurcation. This can produce symptoms by reducing blood flow to the hemisphere supplied or, more commonly, by releasing embolic material.

Emboli can be composed of

Clot

Platelet aggregates

Cholesterol debris.

The carotid bifurcation appears to be susceptible to the development of atherosclerotic plaques. Frequently, severe changes at the carotid bifurcation occur with minimal or no changes present in the common or internal carotid artery. Several investigators have proposed conflicting theories based on hemodynamic observations in various models. High shear stress and fluctuations in shear stress, disordered or turbulent flow, flow separation, and high and low flow velocity has all been implicated. Which of these mechanisms is responsible for plaque formation is not known. Zarins and colleague[1] used a model of the human carotid bifurcation under steady flow and compared its hemodynamics with those of cadaver specimens. They concluded that carotid lesions localize in regions of low flow velocity and flow separation rather than in regions of high velocity and increased shear stress. They used their model to explain the propensity of the outer wall of the carotid sinus opposite the flow divider to develop atherosclerotic plaques. This may have further clinical implications, in that an enlarged carotid bulb after endarterectomy may create a region of reduced flow velocity and increased boundary layer separation, which may favour recurrent plaque deposition.

Once the initial intimal injury is produced by these forces, platelet deposition, smooth muscle cell proliferation, and the slow accumulation of lipoproteins are involved in the reparative process. These eventually lead to plaque

formation, which further alters the hemodynamics of the system and favours further injury.

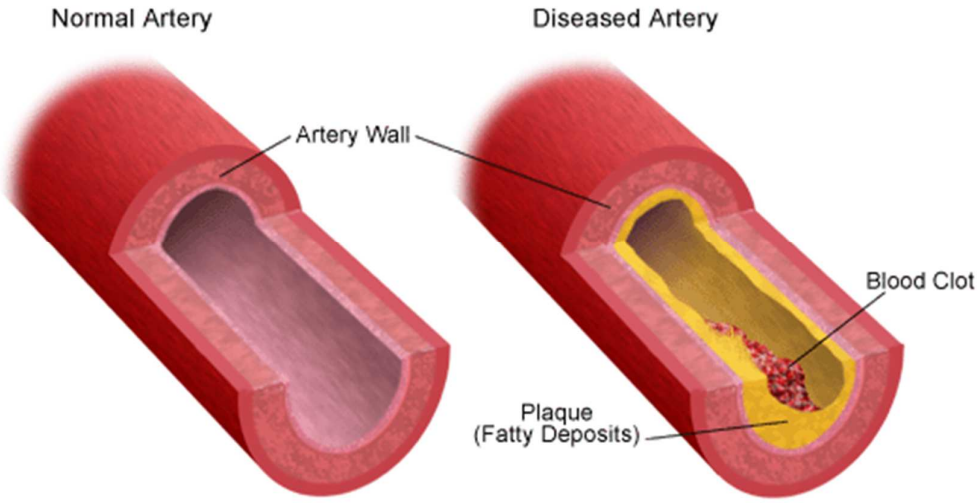



**FIGURE 1**

The contribution of platelets to atheroma development can take several forms. Platelets may adhere to one another, to the diseased vessel, or both; this can lead to thrombus formation. This process may narrow the vessel lumen, or the thrombus may dislodge, resulting in distal embolization. Vasoactive substances stored in granules within the platelet may be released, causing vasospasm and further contributing to compromise of the arterial lumen. The platelets' interaction with collagen, exposed in an injured intima, may include elaboration of a smooth muscle growth factor that can lead to intimal thickening. The activation of enzymes in platelets, by their contact with collagen, initiates the production of highly active prostaglandins. The

production of thromboxane $A_2$ represents the final common pathway of platelet response to diverse stimuli. This substance is a potent stimulant of platelet aggregation and a powerful vasoconstrictor and is believed to be important in the pathophysiology of plaque formation or the development of symptoms from an already established atheroma.

Haemorrhage into a plaque may also play a significant role in the development of symptoms from an atherosclerotic lesion. Imbalances in wall tension secondary to asymmetrical deposition of plaques can lead to sudden plaque fracture and intraplaque hemorrhage. These can lead to sudden expansion of the atheroma, with acute restriction of flow or breakdown of the intimal surface and concomitant embolization. An alternative mechanism for sudden intraplaque hemorrhage may be related to an increase in neovascularity within the plaque substance. Hypertension may be responsible for precipitating rupture of neovascular vessels, leading to intraplaque hemorrhage and expansion. This process may be responsible for a large number of symptomatic lesions. In a prospective evaluation of 79 atheromatous plaques removed from 69 patients undergoing carotid endarterectomy, 49 of 53 (92.5%) symptomatic patients had evidence of intramural hemorrhage. In contrast, only 7 of 26 (27%) asymptomatic patients showed recent or acute intraplaque hemorrhage. Rupture of an atherosclerotic plaque with intraluminal release of atheromatous debris

has also been correlated with acute stroke and internal carotid occlusion in an autopsy study.

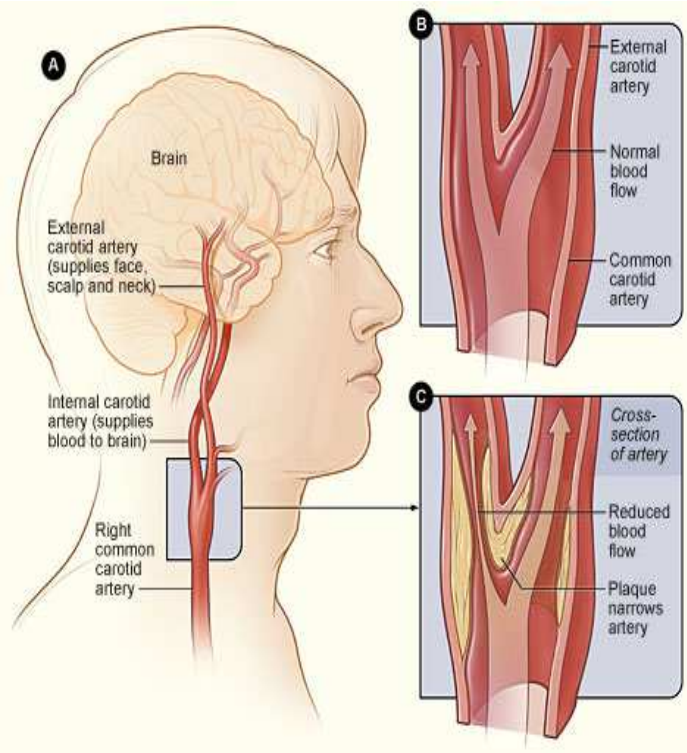



**FIGURE 2-** The common carotid artery bifurcation, the most common site for atherosclerotic plaque deposition. *ECA,* External carotid artery; *ICA,* internal carotid artery.

Extra cranial cerebrovascular disease may also be identified in those who have no symptoms directly attributable to their arterial stenoses. Overall, only 1% of the population over the age of 65 harbors carotid occlusive disease. Yet, in patients with cardiovascular risk factors such as hypertension, hyperlipidemia, and cardiac disease this figure rises substantially to nearly 20%. This is the reasoning behind cerebrovascular screening programs, which allow recognition

of those at highest risk of stroke, followed by the initiation of therapy for stroke-risk reduction.

Usually, the symptoms are found to be unrelated to the carotid arteries, yet a stenosis is identified. When asymptomatic carotid stenoses are identified, some 10-15% will progress to a severe category. Therefore, the management of those with asymptomatic carotid artery stenosis has become a very important issue. Symptomatic carotid occlusive disease consists of transient ischemic attacks (TIA) and stroke, or cerebrovascular accident (CVA). Classically, a TIA is defined as acute neurologic symptoms lasting less than 24 hours that completely resolve. However, the duration usually is measured in minutes, not hours. The term reversible ischemic neurologic deficit (RIND) has been used to describe neurologic symptoms that last longer than 24 hours but then rapidly resolve. CVA is defined as neurologic symptoms lasting longer than 24 hours with evident structural infarction. The term crescendo TIA, or stuttering TIA, is used when TIAs occur more frequently (progressive over 24-48 hours), yet there remains complete reversal of neurologic symptoms in between. Stroke-in-evolution is when there is no resolution of symptoms, but rather they wax and wane indicating ongoing neuron ischemia and neural tissue at risk of infarction. These are highly unstable situations. Symptoms reflective of thromboembolic events due to disease in the carotid artery or anterior circulation include hemiparesis, hemiparesthesias, transient monocular blindness (amaurosis fugax), or difficulties with speech (aphasia).

Approximately 75-80% of patients who suffer a stroke have had no type of preceding transient neurologic symptoms. However, if a patient experiences a TIA, the risk of stroke is significant. Studies have delineated a 30-50% 5-year risk of stroke once TIA occurs. In fact, recent evidence suggests that a significant proportion of this risk occurs within the first several weeks after TIA with, perhaps, a 10-25% risk of CVA within 1 month of the event. Some have even suggested that 5-10% of this risk is within hours of the event. It is, thus, critical to identify and evaluate these patients. Unfortunately, TIAs are not specific for the presence of significant carotid artery stenosis or ulcerated plaques. Only about 50% of patients with TIAs will have a tight, or hemodynamically significant, carotid stenosis (<2 mm; ≥50%), occlusion, or ulcerated plaques. The remaining 50% of patients have thromboembolism from other sources such as the heart, aortic arch, intracranial vascular disease, or no clearly evident etiology. TIAs from alternate site thromboembolism or hypercoagulability also commonly lead to stroke. However, patients with no evident etiology for their TIAs and relatively normal carotid arteries on evaluation usually follow a more benign course; they seldom suffer a stroke. TIAs may be either hemispheric or retinal in nature. In approximately 25% of patients presenting with symptomatic carotid bifurcation atheroma, visual disturbances are the presenting symptom. Amaurosis fugax (AF) is the most common of these ocular manifestations. Transient hemianopias and other subtle visual field defects occur less frequently. Classic amaurosis is described as a

"shade coming down over the eye" for a few seconds to minutes at a time and is due to embolism to the ophthalmic artery. While the natural history of AF is somewhat more benign than hemispheric TIAs it is still significant. The stroke risk once AF arises is roughly 6-8% per year, or roughly half that in those with cerebral TIAs. And, in those experiencing visual symptoms due to cerebrovascular disease, a significant group (25%) will ultimately suffer permanent visual loss.

The importance of identifying those with CVA and cerebrovascular atherosclerosis, particularly within the extracranial arteries, is due to the significance of stroke recurrence. Without treatment, those with CVA will have another stroke at a rate of between 10-20% per year, thus the 5-year gross risk is somewhere between 50% and 100%. The mortality associated with this second CVA is 35%, and events beyond the second are more than 60%. Hence, the institution of therapy is imperative.

Rarely, deterioration in visual acuity may be due to chronic ocular ischemia (COI). Severe bilateral occlusive disease leads to a supply/demand mismatch in the retina with an increase in metabolic demand. COI is the name of the constellation of signs and symptoms related to this. Findings may include eye pain, venous stasis retinopathy, central or branch retinal artery occlusions from stagnant flow, ischemic optic neuropathy, narrowed retinal arteries, retinal microaneurysms, retinal haemorrhages, iris neovascularisation (rubeosis iridis) with neovascular acute angle glaucoma, iris atrophy, corneal oedema, and

cataracts. This syndrome only occurs in 3-4% of those with cerebrovascular disease. Without treatment permanent blindness occurs uniformly. Another rare ocular symptom that may occur is “bright light amaurosis fugax.” This occurs because of the poor retinal blood flow causing complete white out blindness when the retina is stressed, such as going outside into the sunlight. Frequently, the vascular specialist may be asked to comment on the presence of Hollenhorst plaques and retinal artery occlusions seen on fundus examination without evidence of COI. Less than 10% of these patients will have significant carotid stenosis ipsilateral to these findings.

There are a few other uncommon symptoms of cerebrovascular disease that may be attributed to significant carotid occlusive disease. One is jaw claudication with eating due to poor ECA flow to the masseter muscle. Focal seizure activity has been noted due to atheroembolism from carotid artery disease. Pre-syncope or syncope, sometimes called drop-attacks and cognitive impairments, may rarely occur secondary to poor perfusion from significant bilateral cerebrovascular disease.

## Duplex ultrasound

With the advent of noninvasive vascular laboratories and the establishment of duplex ultrasonography, this is the initial imaging modality of choice for most patients in which a diagnosis of carotid artery disease is entertained. Duplex ultrasound combines brightness-mode (B-mode) ultrasound with pulsed-wave Doppler to produce a real time gray-scale image of the arteries, as well as spectral analysis of flow.

Many criteria have been espoused that attempt to identify and quantify the degree of carotid stenosis using duplex ultrasound. This is an ongoing process and requires regular correlation with other imaging modalities in order to solidify each noninvasive laboratory's exactness. When performed by skilled vascular technologists, this imaging approach is quick, sensitive, specific, and highly accurate, and also carries no risk.

Indirect evidence of arch-based and intracranial stenosis may be present but no direct imaging in these areas is possible. Transcranial Doppler may be performed in conjunction to further ascertain intracranial disease, but it cannot delineate lesion anatomy or true disease burden. The authors use the modified University of Washington criteria.

A greater understanding and study of duplex ultrasound in carotid occlusive disease, as well as its ease, has led to sensible surveillance regimens in those

with cerebrovascular disease. This is now standard practice both in those found with moderate carotid stenosis and after carotid surgery.

## COMPUTED TOMOGRAPHY (CT/CTA) AND MAGNETIC RESONANCE ARTERIOGRAPHY (MRI/MRA)

Anatomic definition and direct imaging of the brain, intracranial vasculature, arch branches, and aortic arch are valuable benefits of CTA and MRA. Up to 10% of the time, arch-branch based disease is found to be present. In 2-5% of carotid bifurcation stenoses, either a tandem intracranial stenosis or intracranial aneurysm exists distal to the carotid lesion. Further, the status of the brain and recent or past CVA can be identified, which is particularly important in symptomatic cerebrovascular disease.

With CTA, infarction cannot always be identified immediately as it often takes 24 to 48 hours for evidence of stroke to be present using this imaging modality. A benefit of CTA is the imaging of intracranial bleeding.

Atherosclerotic calcification can limit CTA's ability to characterize stenoses. MRA, on the other hand, using diffusion weighted technology, can illustrate and describe infarction immediately.

A drawback to MRA is its notorious overrepresentation of stenoses.

## ARTERIOGRAPHY

The stroke risk associated with cerebrovascular arteriography is 1-2%. Access site and other complications can occur in up to 3%, which led to the development of other less invasive methods of imaging. Yet, there remain several situations where arteriography is helpful and finalizes cerebrovascular imaging. These include discordant or unreliable noninvasive studies, a high carotid bifurcation, no clear lesion endpoint seen, concern for either intracranial or arch based/great vessel disease, the possibility of nonatherosclerotic etiologies of disease, suspected posterior circulation disease as the symptom cause, recurrent stenosis, and the potential indication for endovascular treatment such as CAS or vertebral origin stenting.

## TREATMENT OF CAROTID OCCLUSIVE DISEASE

## MEDICAL THERAPY

Risk factor modification is clearly indicated in patients with cerebrovascular disease. Many already have risk reduction therapies in place for hypertension, hyperlipidemia, and coronary artery disease at the time of diagnosis of carotid, great vessel, and vertebral artery disease due to the association with other cardiovascular processes.

Statin therapy has been shown to be beneficial in carotid occlusive disease both in primary and post-procedural roles.

Antiplatelet drugs such as aspirin and clopidogrel retard platelet aggregation and may prevent microemboli that cause TIAs and strokes. This has made these agents critical components of maintenance therapy after neurologic events and diagnosis of asymptomatic stenosis. Aspirin reduces the risk of continuing TIAs, stroke, and death by approximately 20%, compared to controls.

In a randomized, blinded trial of clopidogrel (Plavix, Sanofi Pharmaceuticals, Inc., New York, NY, U.S.A.) versus aspirin in patients at risk of ischemic events (CAPRIE), clopidogrel (75 mg daily) reduced the relative risk for ischemic stroke, myocardial infarction and vascular death by 24%.

After carotid endarterectomy, antiplatelet therapy reduces risk of stroke and to a lesser degree restenosis. It appears likely that antiplatelet therapies modestly reduce the risk of stroke in both symptomatic and asymptomatic individuals with cerebrovascular disease, and are indicated with minimal bleeding risk.

Heparin or warfarin sodium can also control TIAs in at least 90% of patients with recent onset. Warfarin also has proved effective in reducing serious cerebral infarct from 45% in untreated patients to 24% in treated individuals over 5 years.

Of course, the main disadvantage of long-term Coumadin therapy is compliance and bleeding complications in about 15% of patients. Indeed, the current

recommendations from the multispecialty guidelines council has recommended heparin not be used in acute stroke due to the hemorrhagic risk.

## SURGICAL THERAPY

During CEA the carotid artery is clamped and opened, and the atherosclerotic plaque is removed. Large, multicenter prospective, randomized trials comparing this operation plus antiplatelet therapy to antiplatelet therapy alone have provided many insights into this surgical option. In patients with a hemodynamically significant carotid stenosis, who have had a TIA or a stabilized, nondisabling stroke and are candidates for operation, CEA reduces the risk of recurrent stroke. This was clarified in both the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery trial (ECST). The Veterans Affairs Trial 309 (VA 309) also found a trend favouring surgery, but was halted when the initial results of NASCET and ECST were reported. NASCET's evaluation of those with high-grade (≥70%) stenosis was stopped early as the risk of stroke at 2 years was 26% versus 9% ($p<0.001$), and mortality 12% versus 5% ($p<0.01$), in the medical and surgical arms, respectively. Stroke-risk reduction increased as the degree of stenosis became greater. Thus, those with the most significant degree of stenosis gleaned the highest degree of absolute benefit. For those with carotid stenosis of 50-69%, NASCET revealed a significant reduction in ipsilateral

stroke (15.7% vs. 22.2%; p = 0.045) and any stroke or death (33.3% vs. 43.3%; p = 0.005) at CEA 5 years. Although still statistically noteworthy, the absolute risk reduction was less than in those with higher-grade stenoses and was not as evident until the later points of follow-up.

In ECST and the VA 309 similar outcomes were found. Data generated from the pooling of these three trials has confirmed the stepwise augmentation in stroke-risk reduction with CEA by increasing stenosis degree. Carotid stenosis of 50% was confirmed to be the point at which CEA yields significant absolute 5-year stroke-risk reduction compared with medical therapy. Above 60-70% was the degree to which significant 3-year absolute stroke-risk reduction occurred. Benefits of CEA in the symptomatic prospective, randomized trials appear to be greatest in men, those with recent stroke, and hemispheric symptoms.

## CAROTID ARTERY STENTING

Although the medical and surgical treatment of carotid occlusive disease has been well studied and effective treatment paradigms developed, the last decade has seen the emergence of endovascular therapies as an alternative for treatment of cerebrovascular diseases. CAS has been promoted as the preferred option in those who are “high-risk” for CEA. There has been much debate as to what constitutes high-risk individuals in this relatively low-risk operation, and

ongoing deliberations focus on what clinical factors may produce a scenario when CAS may be favoured over other modalities of treatment.

To this end many investigations have focused on noninferiority of CAS versus CEA in certain patient subgroups. Problems with these have been encountered, and center around differences in indications and devices used. Most have been industry sponsored and are specific to stent and embolic protection devices, in addition to combining endpoints and patient presentations.

The most stirring study to date is the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial. This study was supported by Cordis Endovascular (a branch of Johnson & Johnson) and Cordis stents and embolic protection devices were used. It pitted CEA against CAS with embolic protection in those who were symptomatic with a ≥50% stenosis or asymptomatic with a ≥80%, and had features that would place them at high risk for CEA.

The main outcomes of stroke and death were not statistically different at 30 days and 1 year, thus CAS was not found to be inferior to CEA. However, when this endpoint was combined further to include MI, there was a trend favouring CAS in the perioperative 30-day period, and this added to the incidence of stroke or death in 1 year was reported to favour CAS (12% vs. 20%; $p = 0.05$). The occurrence of cranial nerve palsies was significantly less with CAS and the need for revascularization of the carotid artery within 1 year of the treatment was statistically higher in those receiving CEA (4.6% vs. 0.7%; $p = 0.04$).This

seems to indicate that CAS is competitive with CEA in the early and midterm treatment of carotid stenosis . Against the background of conflict in the prior literature, the U. S. Food and Drug Administration used this report to usher in the era of approval of CAS devices. There are justified criticisms of SAPPHIRE concerning both the trial endpoints and the enrollment process, but this is the best information we have to date. The late stroke-risk reduction achieved and the later restenosis with stenting remain unknown.

These are critical pieces of information that are needed as the physiologic outcome of CEA and CAS may ultimately be different. CEA removes the embolic source and relies on appropriate and "normal" healing of the endarterectomy and CAS pushes, opens, and constrains the embolic source against the diseased arterial wall.

Stroke after CAS seems to occur more often in the contralateral hemisphere compared to CEA, which is likely due to arch manipulation. Embolic protection devices do make a difference in the embolic rate during CAS.

Current indications for CAS are being better defined. Anatomic factors in the carotid artery, aortic arch, descending aorta, and iliofemoral systems are very germane and may alter, or support, one treatment plan over another. Other issues, such as prior neck pathology requiring radiation or tracheostomy, are more easily dealt with using CAS. Those with poor cardiopulmonary reserve may be better served with CAS. If the procedure seems anatomically feasible with minimal structural prohibitions, certain indications have become clearer.

Indications are:

Restenosis

Prior radical neck surgery

An adverse neck due to tracheostomy, radiation

High carotid bifurcations at the c1-2 level

Significant cardiopulmonary comorbidities

It also appears that those patients who are 80 years of age or older do worse with CAS. This may be due to more atherosclerotic disease and arch angulation in older people.

## PROSPECTIVE RANDOMISED TRIALS

Despite retrospective data analysis clearly demonstrating the superiority of carotid endarterectomy over medical management in regard to stroke prevention, a number of well-meaning critics point out that retrospective data analysis can be misleading. Retrospective studies compare surgical results with available natural history data. The natural history of a particular disease process can change, often for the better, making the basis of comparison invalid. Likewise, retrospective reviews are often performed in centers of excellence, where surgical complication rates may be lower than the actual risk of operation in the community. For this reason, several prospective, randomized trials were initiated in North America and Europe. The objective of these trials was to scientifically evaluate the efficacy of carotid endarterectomy in preventing stroke for a variety of indications when compared with a true, contemporary control group. The trials can generally be categorized into two major classifications: asymptomatic and symptomatic carotid artery disease.

Three asymptomatic trials have completed their data acquisition and reported results: the Veterans Administration Asymptomatic Carotid Stenosis Study, ACAS, and the European Asymptomatic Carotid Surgery Trial. Three symptomatic trials have been completed: NASCET, the Medical Research

Council European Carotid Surgery Trial (ECST), and the Veterans Administration Symptomatic Trial (VAST).

## ASYMPTOMATIC TRIALS

### Veterans Administration Asymptomatic Carotid Stenosis Study

Ten Veterans Administration (VA) medical centers entered into a prospective, randomized trial designed to test the hypothesis that carotid endarterectomy plus best medical management (aspirin and risk factor control) would result in fewer TIAs than treatment with the best medical management alone. The design of the study was published in 1986.Angiography was performed in 713 patients, 3 of whom (0.4%) sustained a neurologic deficit.[

A total of 444 patients were randomized over a 54-month interval. In the surgical group, 211 carotid endarterectomies were performed; these patients also received aspirin therapy. In the medical group, 233 patients were treated with aspirin alone. The study spanned a total of 8 years. The 30-day mortality rate for the surgery group was 1.9%, and the incidence of stroke was 2.4%. The combined stroke and mortality rate was 4.3%.

The data analysis demonstrated that all neurologic events (stroke, TIA, amaurosis fugax) in any distribution (including the study artery), combined with deaths, totalled 30 in the carotid endarterectomy group, which represented

14.2% of that population. For the patients treated medically, a total of 55 events occurred, for an event rate of 23.6%. This difference was statistically significant ($p < 0.006$). When the data were analyzed for deaths plus ipsilateral events only, a total of 21 events occurred in the carotid endarterectomy group, for an incidence of 10%; in contrast, there were 46 events in the medically treated group, for an incidence of 19.7%. Once again, this difference was statistically significant ($p < 0.002$). Although the study was not designed to look at stroke alone, this was done retrospectively. A total of 10 strokes occurred in the carotid endarterectomy group ipsilateral to the study artery, for an incidence of 4.7%. A total of 20 strokes occurred in the study artery distribution in the medically treated group, for an incidence of 8.6%. This difference fell just short of statistical significance ($p = 0.056$), probably because of the small sample size. There was no difference in survival rate between the surgically and medically treated groups. This is not surprising, because the major cause of death in this patient group is MI, and prevention of stroke is unlikely to have a beneficial effect on reducing fatal MI. This lack of difference in survival between the surgically and medically treated groups should not be considered a negative factor when interpreting data results, because the objective of operation is to maintain the patient stroke free during his or her remaining lifetime.

## Asymptomatic Carotid Atherosclerosis Study

The ACAS, sponsored by the National Institutes of Health (NIH), was the largest multicenter (34 centers), North American, prospective, randomized trial of surgery for asymptomatic carotid stenosis. It tested the hypothesis that carotid endarterectomy plus aspirin and risk factor control would result in fewer TIAs, strokes, and deaths than would aspirin and risk factor control alone.

The design of the study was published in 1989. Initially, 1500 patients were to be randomized, with TIA included as an end point. After criticism of the VA study, the protocol was amended to have stroke and death as the end points. The Data Safety and Monitoring Committee of the NIH gave permission to increase the sample size from 1500 to 1800 patients.

In December 1994, the committee called a halt to the study and informed the investigators, and subsequently the public, that an end point had been reached in favour of carotid endarterectomy, and a full report was published. A total of 1662 patients with diameter-reducing lesions of 60% or greater (as measured by angiography using the North American method; see later) were randomly allocated to receive carotid endarterectomy plus best medical management, including aspirin; the control group received best medical management alone. After a mean follow-up of 2.7 years (4657 patient-years of observation), the

aggregate risk over 5 years for ipsilateral stroke, any perioperative stroke, and death was 5.1% for surgical patients and 11% for patients treated medically. The results of surgery, including perioperative morbidity and mortality, reduced the risk of death and stroke by 5.9% absolutely and yielded a 53% risk reduction. This difference was highly significant.

The beneficial effect of surgery in asymptomatic patients was due in large part to the low 30-day perioperative stroke morbidity and mortality. Before the study began, the surgical management committee for ACAS established criteria to audit surgeons who wished to participate in the study. Validation of the audit method was possible on conclusion of the study. Among 825 patients randomized to surgery, the stroke morbidity and mortality rate within 30 days of randomization was 2.3%. However, this included a stroke morbidity and mortality of 1.2% for preoperative angiography. Because of the intent-to-treat design, the angiographic complications were charged to surgery. Of the 724 patients who actually had carotid endarterectomy, mortality was 0.14%, and the stroke rate was 1.38%. Thus, the true 30-day stroke morbidity and mortality rate was 1.52%.

## Asymptomatic Carotid Surgery Trial (ASCT)

A group of European investigators, headed by a team from the United Kingdom, embarked on yet another trial. However, included in their trial were methods designed to try to identify a higher-risk group of patients. The investigators reported their results in 2004. A total of 3128 asymptomatic patients with carotid artery stenoses of 70% or greater, as measured by ultrasonography, were entered into the trial from 1993 through 2003. The patients were equally randomized between immediate carotid endarterectomy and indefinite deferral of operation.

The 30-day risk of stroke or death in the surgical group was 3.1%. When analyzing the 5-year results of the two groups, the stroke risk, excluding perioperative events, was 3.8% in the surgical group, versus 11% in the nonsurgical group ($p < 0.0001$). Half the stroke events were disabling or fatal. If perioperative events were included, the 5-year stroke rate in the two groups was 6.4% versus 11.8% ($p < 0.0001$). Comparing fatal or disabling strokes, the event rate was 3.5% in the surgical group versus 6.1% in the nonsurgical group. The investigators found that the results were significant for both men and women when analyzed separately. The authors concluded that, in asymptomatic patients 75 years of age or younger with a diameter-reducing stenosis of 70% or greater as measured by ultrasonography, immediate carotid endarterectomy reduced the net stroke risk by half, from about 12% in the control group to 6%

(including a 3% perioperative hazard) in the surgical group. Furthermore, half of the 5-year benefit involved the prevention of disabling or fatal strokes.

## SYMPTOMATIC TRIALS

### North American Symptomatic Carotid Endarterectomy Trial

The NASCET was a large prospective trial designed to test the hypothesis that symptomatic patients (those with TIA or prior mild stroke) with ipsilateral carotid stenosis (30% to 99%) have fewer fatal and nonfatal strokes after carotid endarterectomy than do patients treated with medical management alone, including aspirin. Investigators anticipated that approximately 3000 patients would be randomly allocated to receive either medical or surgical management and monitored for a minimum of 5 years. The NASCET was also stratified to study two subsets of patients as a function of the degree of carotid occlusive disease: those with 70% to 99% stenosis and those with more moderate lesions ranging from 30% to 69% stenosis.[ Included in the design of the trial and required by the granting institution (the NIH) was the establishment of an oversight committee that was responsible for reviewing the results of the data from time to time and calling a halt to the study if a clear difference was observed between the two groups.

On February 25, 1991, a clinical alert was issued by the oversight committee, which reported that a clear difference had developed between the two groups, indicating that carotid endarterectomy was superior to medical management in the high-grade stenosis category (70% to 99%). No clear difference had yet occurred in the moderate stenosis group (30% to 69%), and the latter continued to enter patients for randomization.

In the high-grade stenosis category, 295 patients received medical management and 300 patients received surgical management. Sixteen of the medically treated patients (5.4%) actually crossed over to surgery, but because of the "intent-to-treat" design, these patients continued to be analyzed as if they were managed medically, despite their operations. Crossovers become important if the group that patients are leaving is in fact a disadvantaged group, as is the case in this study.

The 30-day operative morbidity and stroke mortality rate for patients managed surgically was 5%. The analysis at the end of 18 months of follow-up, which led the oversight committee to halt this arm of the study. In the surgical group, a 7% incidence of fatal and nonfatal strokes occurred (including perioperative morbidity and mortality). In the medical group, a 24% incidence of fatal and nonfatal strokes occurred. The difference was highly statistically significant ($p < 0.001$). This represents an absolute risk reduction of 17% in favour of surgical

management and a relative risk reduction of 71% with surgical management versus medical management at the end of 18 months.

A surprising finding occurred when the mortality rates were analyzed. To date, no study had shown that carotid endarterectomy patients enjoy greater longevity than those treated medically. However, at the end of 18 months, the mortality rate among the medically treated group was 12%, in contrast to 5% for the surgically treated group. Once again, this difference was statistically significant ($p < 0.01$). This indicates a relative mortality risk reduction of 58% in favour of carotid endarterectomy. Further analysis demonstrated that for every 10% increase in stenosis between 70% and 99%, a progressive increase occurred in morbidity and mortality in the control group.

The NASCET investigators reported their results in the moderate stenosis group (30% to 69%) in 1998. They demonstrated a beneficial effect of surgery in the 50% to 69% stenosis group but not in those patients with less than 50% stenosis. The 30-day mortality and disabling stroke rate was 2.7%, and the nondisabling stroke rate was 4%, for a total of 6.7%. The 5-year rate for ipsilateral stroke in the surgical group was 15.7%, compared with 22% for patients treated medically. Thus, 15 patients would need to undergo carotid endarterectomy to prevent one stroke over a 5-year interval.

## Medical Research Council European Carotid Surgery Trial

The ECST was a large multicenter trial of symptomatic patients with carotid artery disease that was carried out over a 10-year period and reported at approximately the same time as the NASCET. It confirmed the NASCET results reported to date. A total of 2518 patients were randomized over 10 years, providing a mean follow-up of 3 years. This trial stratified the data into three groups: mild stenosis (10% to 29%), moderate stenosis (30% to 69%), and severe stenosis (70% to 99%). In the mild stenosis category, no apparent benefit was evident for carotid endarterectomy compared with the risk of operation. However, in the severe stenosis category, a highly significant benefit in favour of operation was evident. Carotid endarterectomy, despite a 7.5% risk of death and stroke in the perioperative interval, resulted in a six fold reduction in subsequent strokes over a 3-year interval. This difference was highly statistically significant ($p < 0.0001$).

One interesting and important difference has come to light between NASCET and ECST: they have different methods of measuring carotid stenosis. In the European method, where *R* is minimal residual lumen diameter through the stenosis, and *B* is the projected diameter of the carotid bulb. This cannot actually be visualized because it is occupied by plaque, therefore an imaginary line is drawn to outline what is believed to be the bulb.

NASCET uses a method common in North America and was previously described in the VA asymptomatic trial. In this method, where *D* is the diameter of the normal internal carotid artery where the walls become parallel.

The result of this difference is most apparent for moderate stenosis, for which the European method appears to greatly overestimate the percentage of stenosis. Eliasziw and colleagues  compared the same angiograms using the European and North American methods.

**Comparison of Carotid Stenosis Estimated by European and North  American Methods**

| Percent Stenosis, European | Percent Stenosis, North American |
|---|---|
| 60 | 18 |
| 70 | 40 |
| 80 | 61 |
| 90 | 80 |

*Data from Eliasziw M, Smith RF, Singh N, et al: Further comments on the measurements of carotid stenosis from angiograms. Stroke 25:2445–2449, 1994.*

The ECST found significant benefit of carotid endarterectomy in patients with stenosis of 60% to 90%, which corroborated the results in the NASCET moderate stenosis group. The ECST reported no benefit of surgery in the 30% to 69% group as measured by the European method. This is not surprising, because a 69% ECST stenosis is only a 40% stenosis as measured by the North American method.

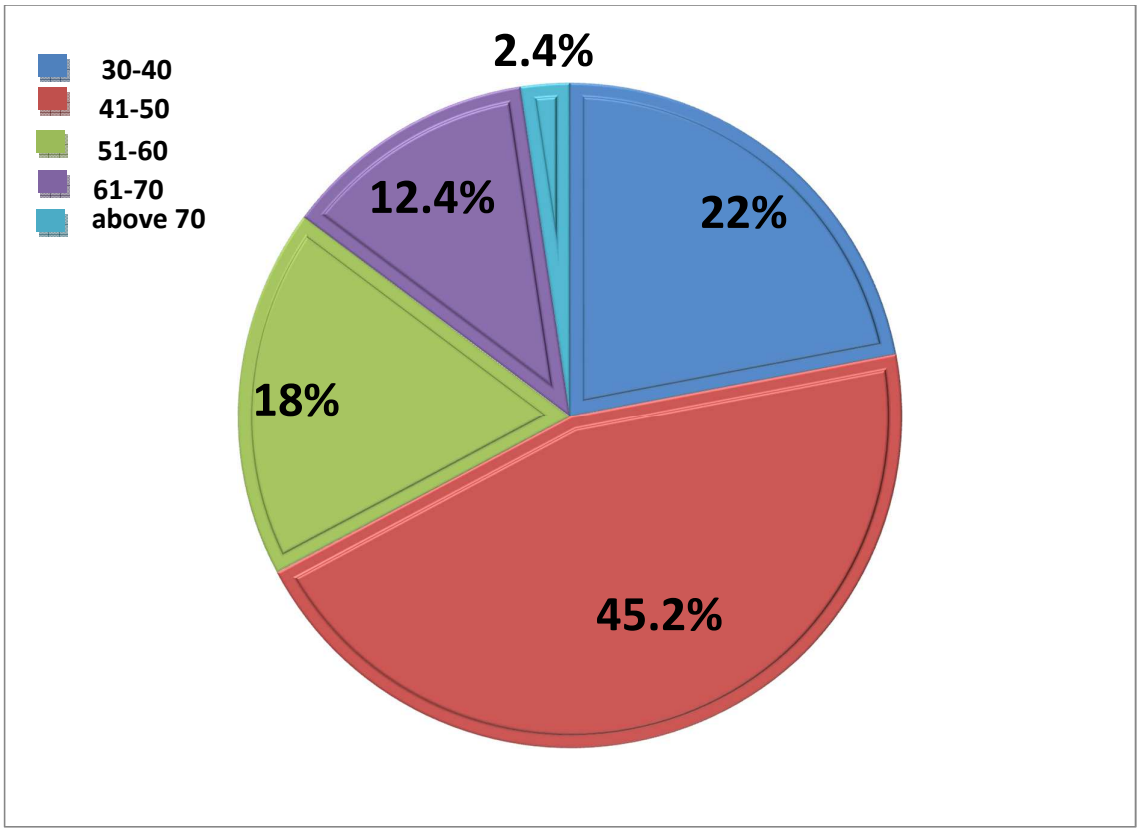
**Veterans Administration Symptomatic Trial**

The VA symptomatic trial was a prospective, randomized trial designed to test the hypothesis that patients with greater than 50% ipsilateral internal carotid artery stenosis who were experiencing symptoms (including transient cerebral ischemia and mild stroke) would have fewer neurologic events (including cerebral infarction and crescendo TIAs) in the vascular distribution of the study artery after carotid endarterectomy plus best medical management than those receiving best medical management alone. This study was just getting under way when the results of the ECST and NASCET were reported, which led to its being halted earlier than anticipated. Nonetheless, 189 patients with symptomatic carotid stenoses were randomly allocated to receive either medical or surgical management. When the results were analyzed with a mean follow-up of 11.9 months, 7.7% of the patients randomized to surgical care had

experienced stroke or crescendo TIAs during the perioperative or follow-up interval. In contrast, those patients randomized to medical management alone experienced a 19.4% incidence of stroke or crescendo TIAs. This difference was statistically significant ($p$ = 0.01). The benefit of operation became apparent within 2 months of randomization.

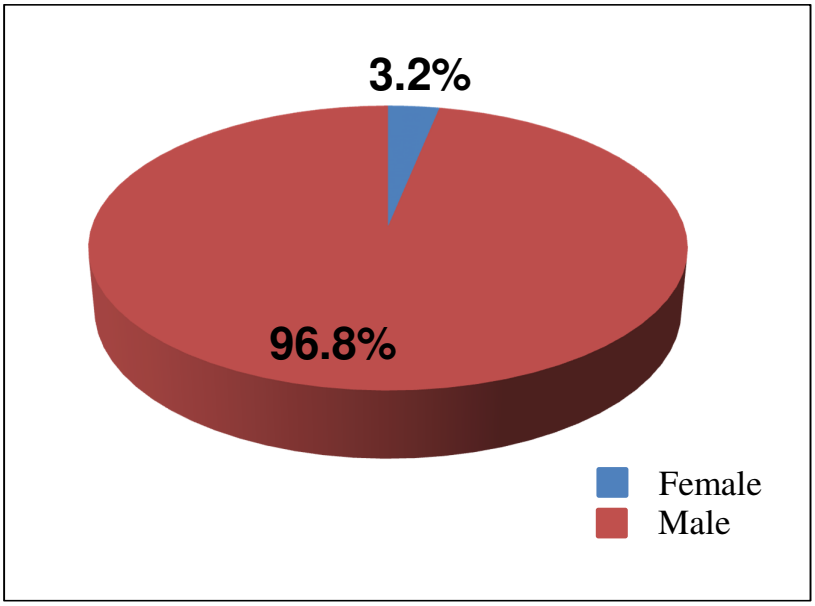
## OBSERVATION AND RESULTS

### AGE



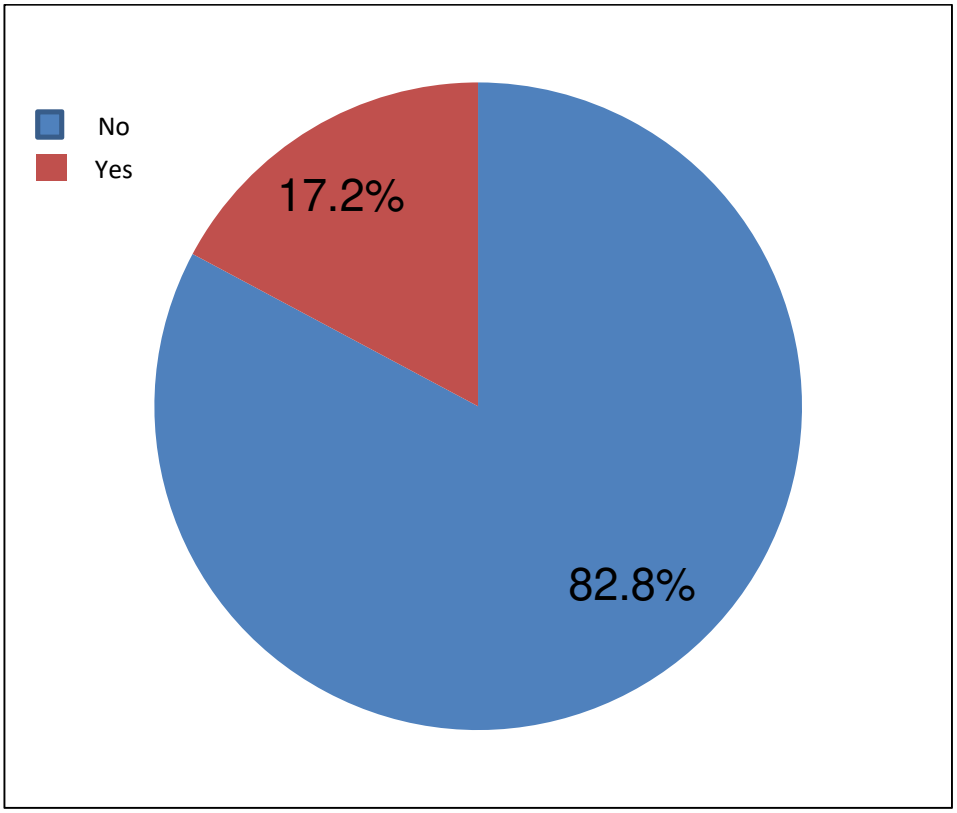

| AGE | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|
| 30 - 40 | 55 | 22.0 | 22.0 | 22.0 |
| 41 - 50 | 113 | 45.2 | 45.2 | 67.2 |
| 51 - 60 | 45 | 18.0 | 18.0 | 85.2 |
| 61 - 70 | 31 | 12.4 | 12.4 | 97.6 |
| ABOVE 70 | 6 | 2.4 | 2.4 | 100.0 |
| Total | 250 | 100.0 | 100.0 | |

**Sex**



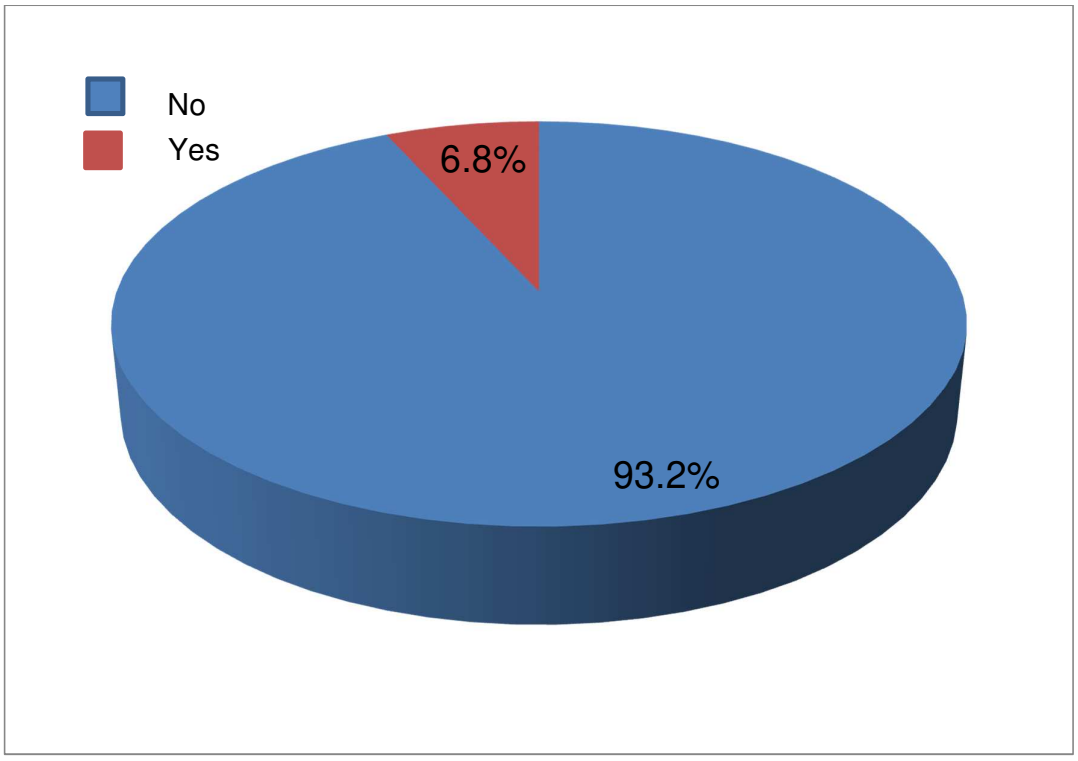

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Sex | F | 8 | 3.2 | 3.2 | 3.2 |
| | M | 242 | 96.8 | 96.8 | 100.0 |
| | Total | 250 | 100.0 | 100.0 | |

**DM**



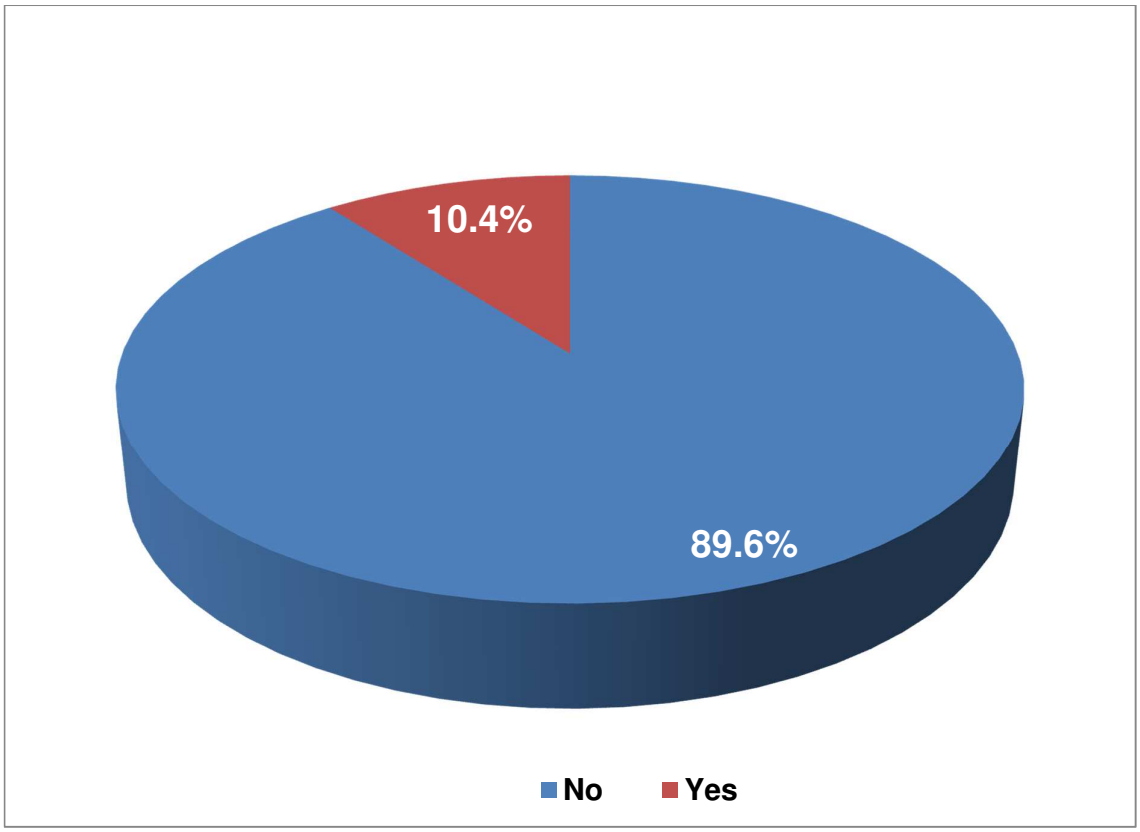

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| DM | No | 207 | 82.8 | 82.8 | 82.8 |
| | Yes | 43 | 17.2 | 17.2 | 100.0 |
| | Total | 250 | 100.0 | 100.0 | |

## HYPERTENSION



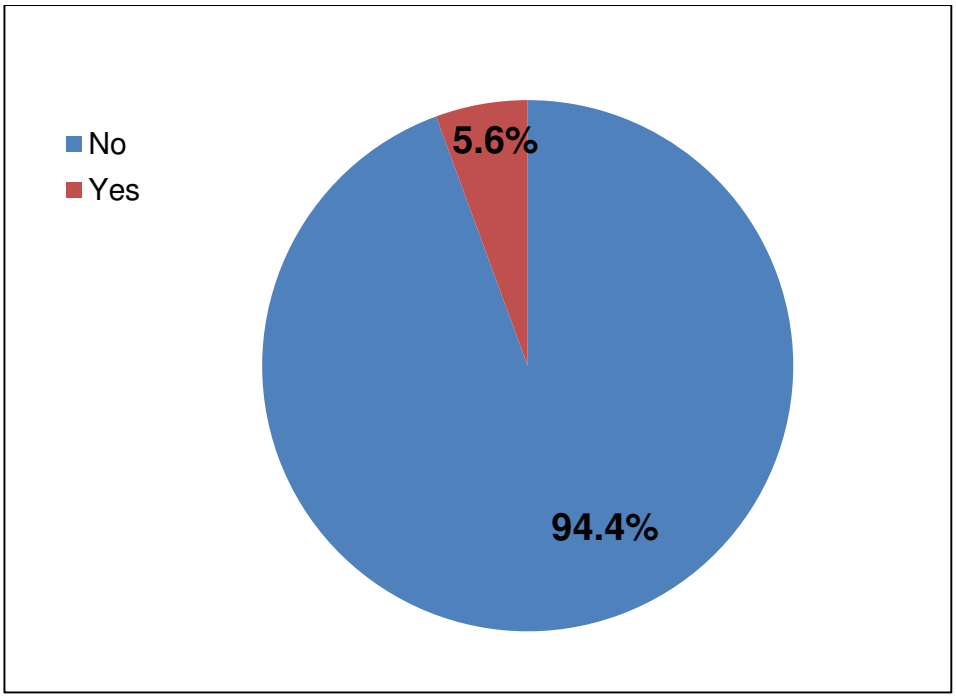

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| HT | No | 233 | 93.2 | 93.2 | 93.2 |
| | Yes | 17 | 6.8 | 6.8 | 100.0 |
| | Total | 250 | 100.0 | 100.0 | |

**CAD**



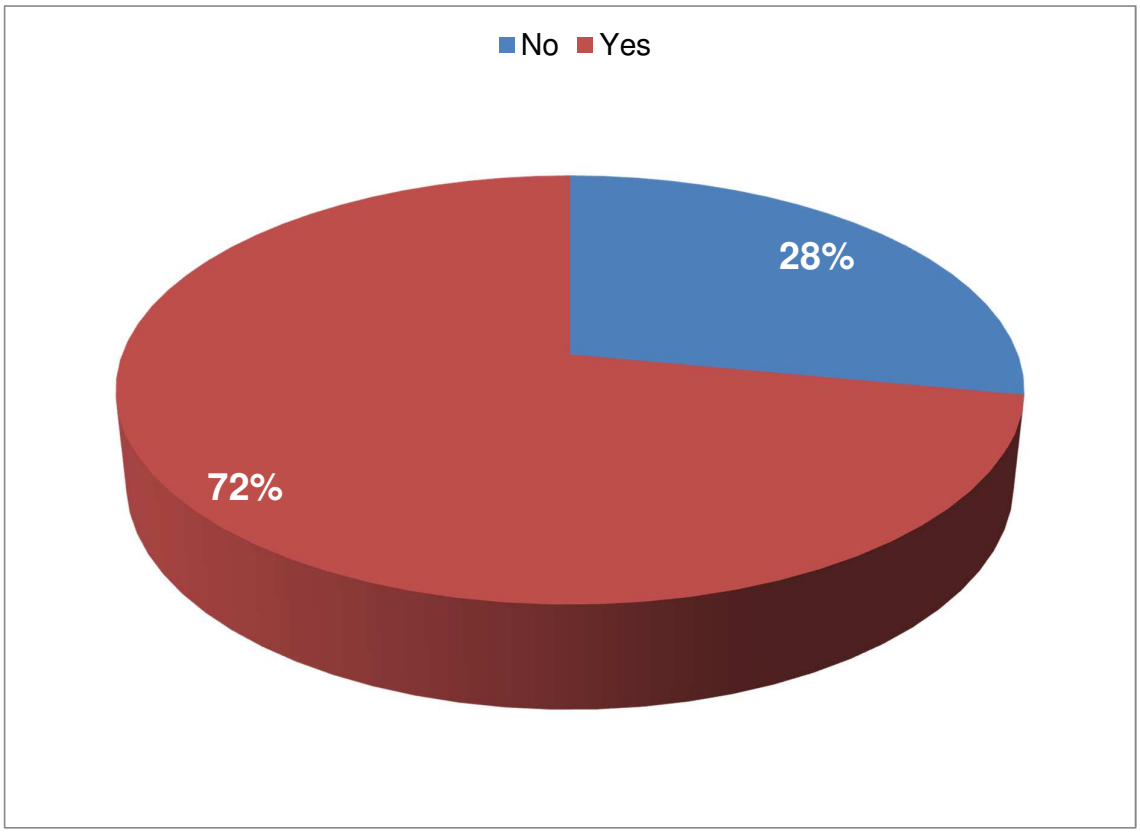

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| CAD | No | 224 | 89.6 | 89.6 | 89.6 |
| | Yes | 26 | 10.4 | 10.4 | 100.0 |
| | Total | 250 | 100.0 | 100.0 | |

## DYSLIPIDEMIA



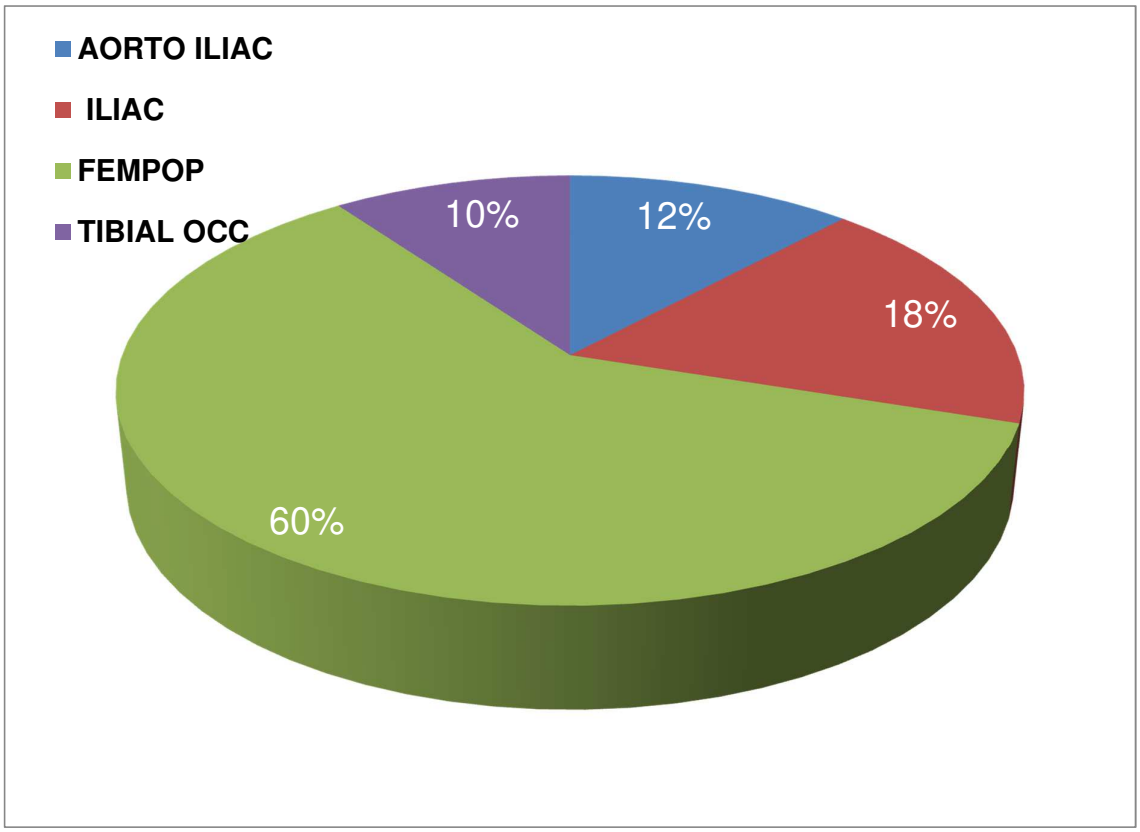

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Dyslipdemia | No | 236 | 94.4 | 94.4 | 94.4 |
| | Yes | 14 | 5.6 | 5.6 | 100.0 |
| | Total | 250 | 100.0 | 100.0 | |

## SMOKER



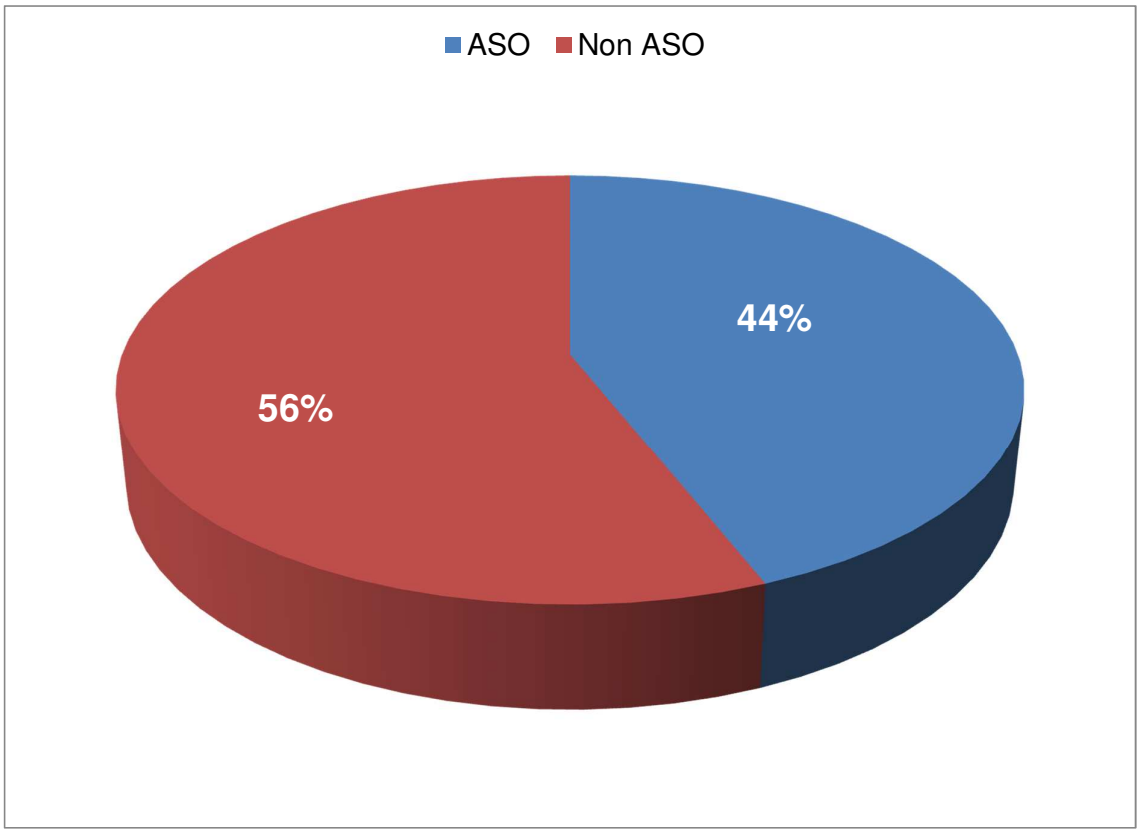

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Smoker | No | 70 | 28.0 | 28.0 | 28.0 |
| | Yes | 180 | 72.0 | 72.0 | 100.0 |
| | Total | 250 | 100.0 | 100.0 | |

## LEVEL OF OCCLUSION



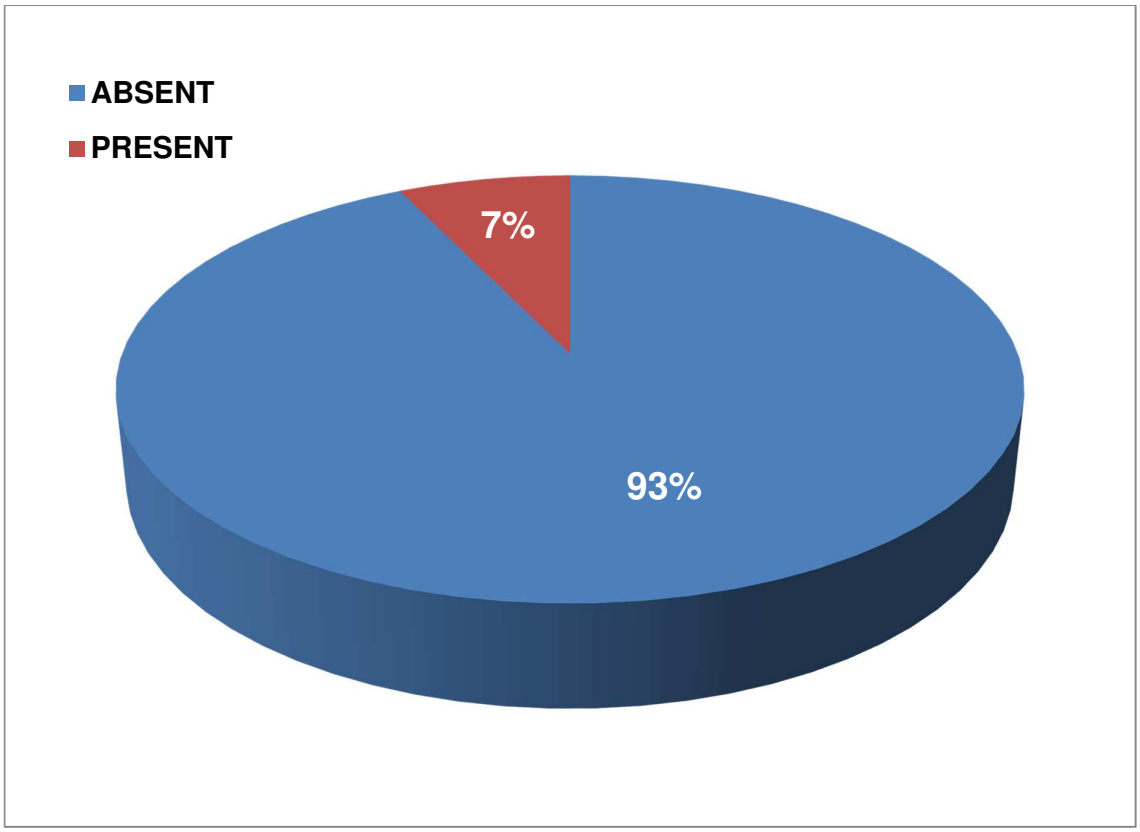

| | | Frequency | Percent |
|---|---|---|---|
| Level of occlusion | AORTO ILIAC | 30 | 8.0 |
| | ILIAC | 45 | 4.0 |
| | FEMPOP | 150 | 70.0 |
| | TIBIAL OCC | 25 | 10.0 |
| | Total | 250 | 100.0 |

## ETIOLOGY



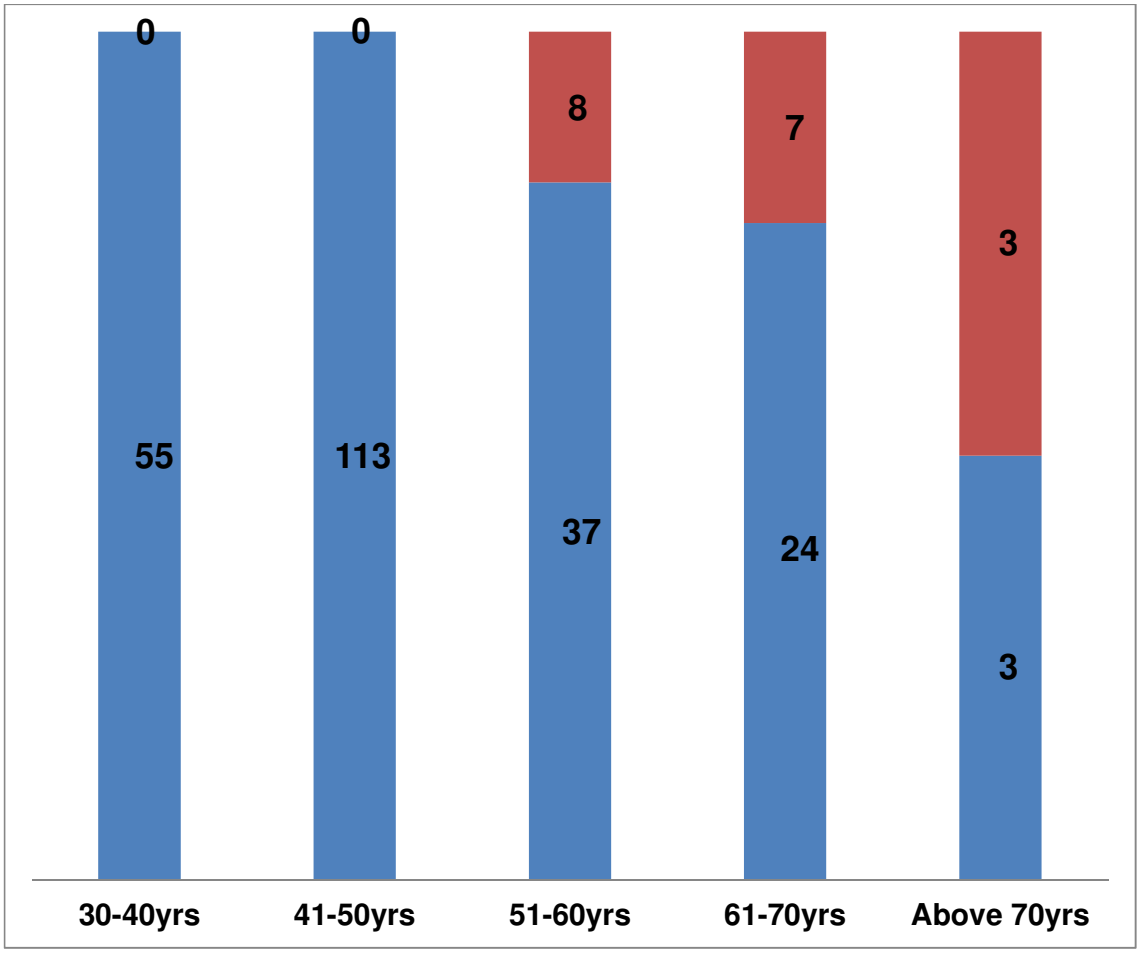

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | ASO | 110 | 44.0 | 44.0 | 44.0 |
| | NON ASO | 140 | 56.0 | 56.0 | 100.0 |
| | Total | 250 | 100.0 | 100.0 | |

## CAROTID DISEASE

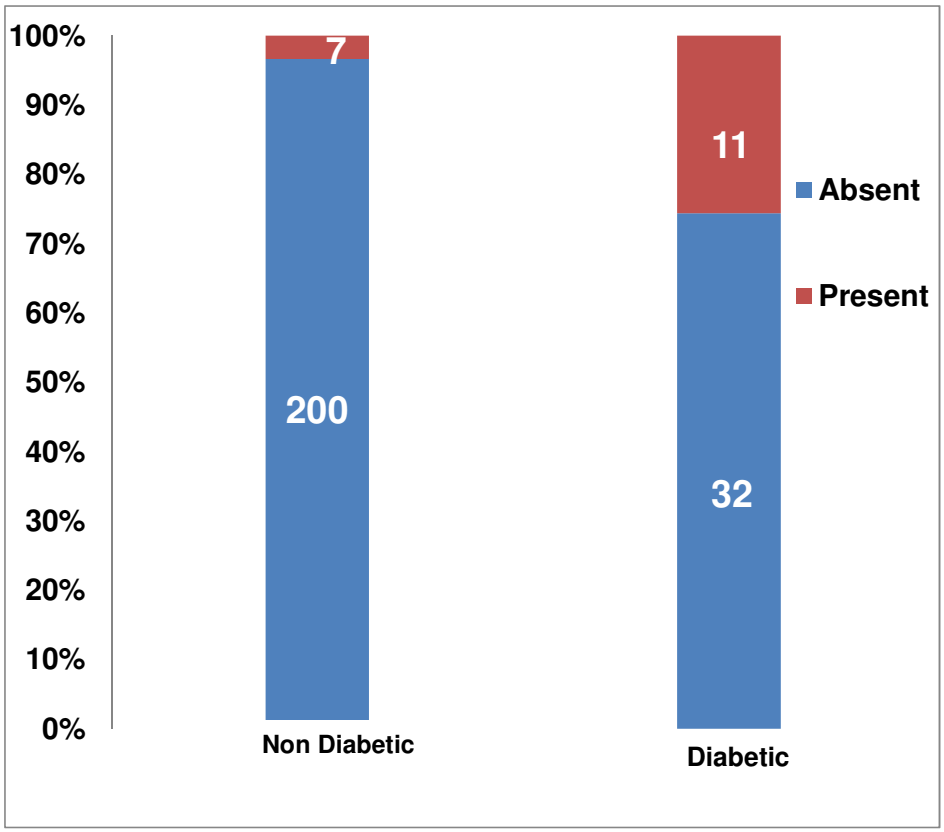



| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Carotid Disease | ABSENT | 232 | 92.8 | 92.8 | 92.8 |
| | PRESENT | 18 | 7.2 | 7.2 | 100.0 |
| | Total | 250 | 100.0 | 100.0 | |

## AGE & CAROTID DISEASE

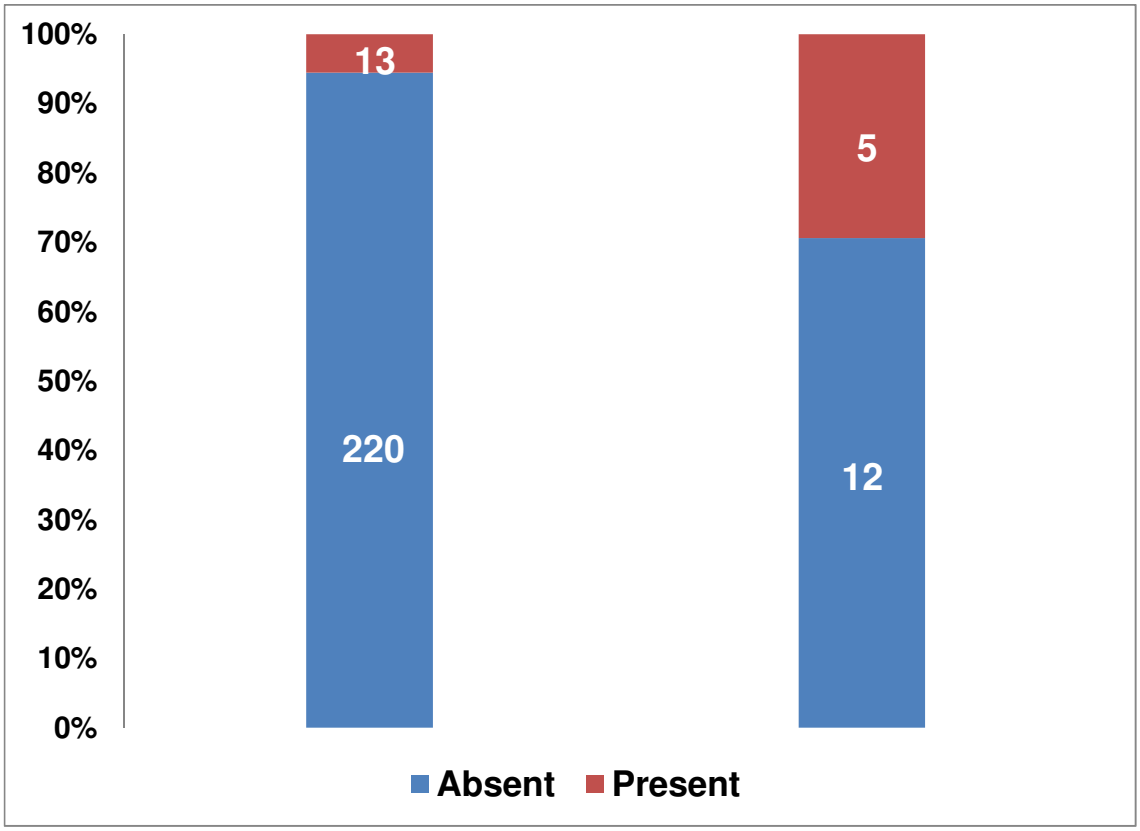


# DIABETIC MELLITUS & CAROTID DISEASE



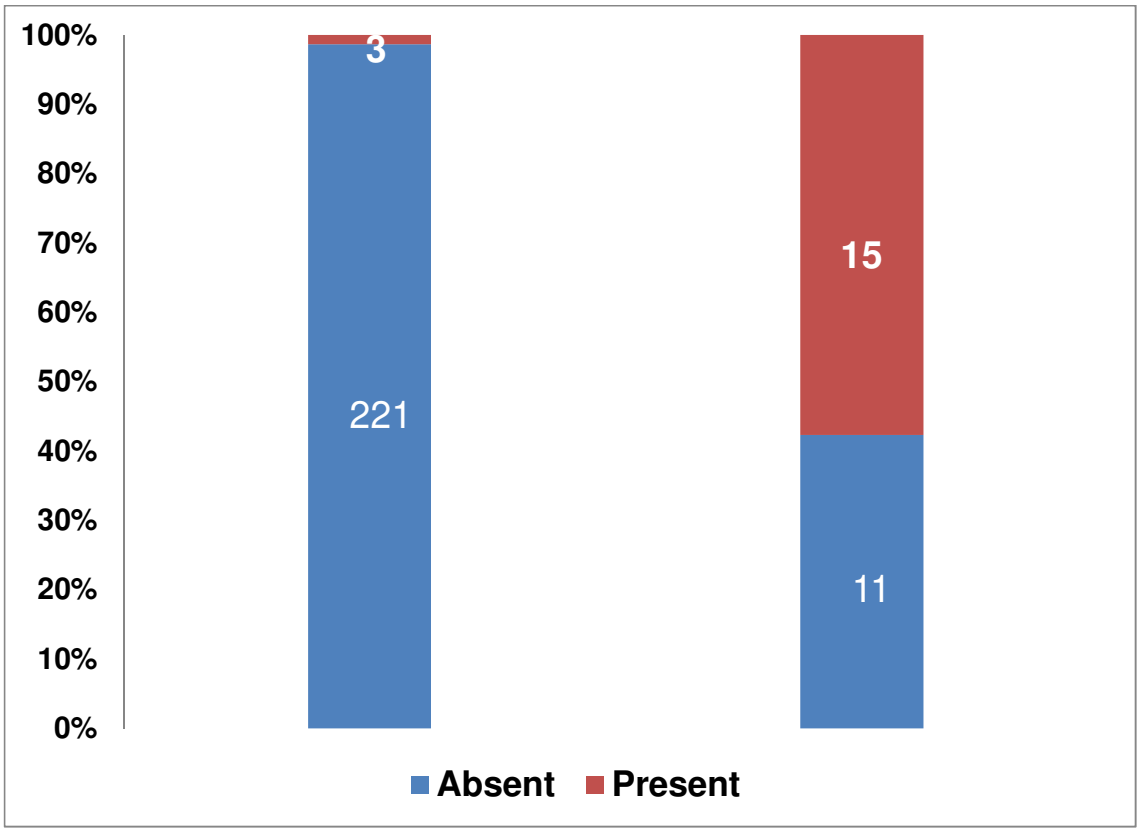

| | | | Carotid disease | | |
|---|---|---|---|---|---|
| | | | Absent | Present | Total |
| DM | No | Count | 200 | 7 | 207 |
| | | % within DM | 96.6% | 3.4% | 100.0% |
| | Yes | Count | 32 | 11 | 43 |
| | | % within DM | 74.4% | 25.6% | 100.0% |
| | Total | Count | 232 | 18 | 250 |
| | | % within DM | 92.8% | 7.2% | 100.0% |

## HYPERTENSION & CAROTID DISEASE



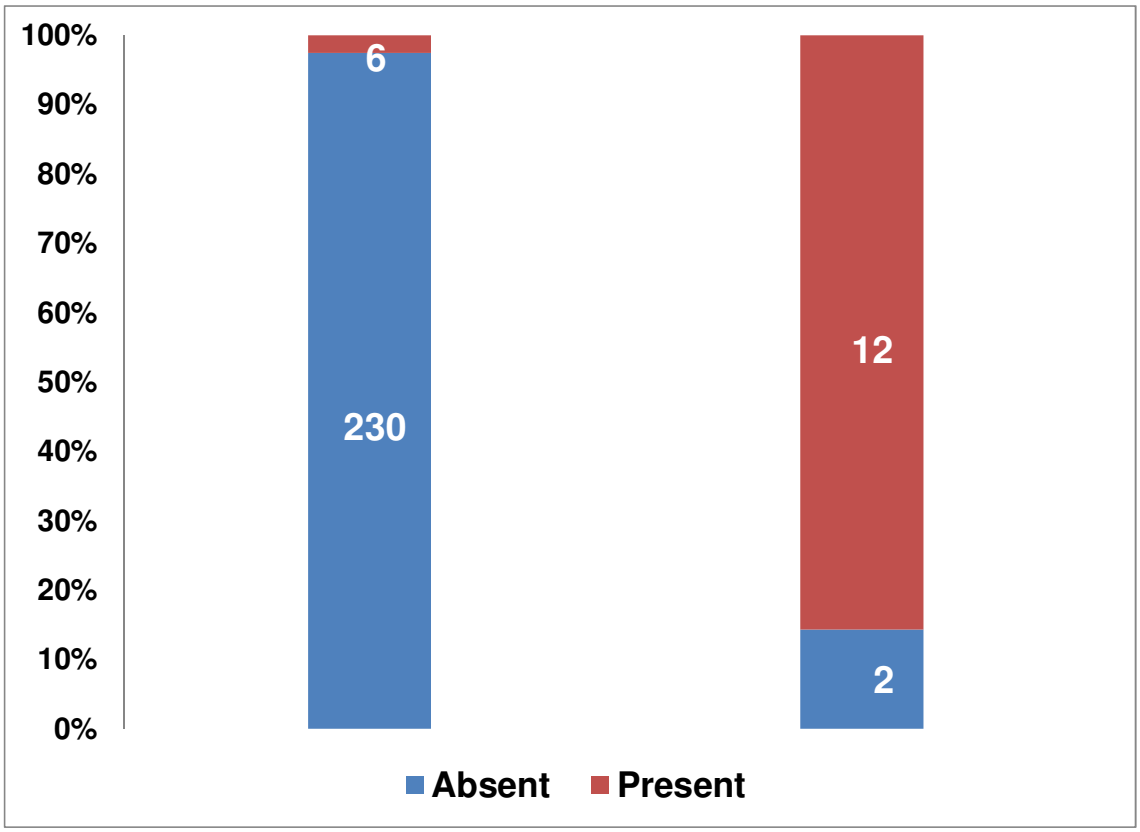

| | | | Carotid Disease | | |
|---|---|---|---|---|---|
| | | | Absent | Present | Total |
| HT | No | Count | 220 | 13 | 233 |
| | | % within HT | 94.4% | 5.6% | 100.0% |
| | Yes | Count | 12 | 5 | 17 |
| | | % within HT | 70.6% | 29.4% | 100.0% |
| | Total | Count | 232 | 18 | 250 |
| | | % within HT | 92.8% | 7.2% | 100.0% |

## CAD & CAROTID DISEASE



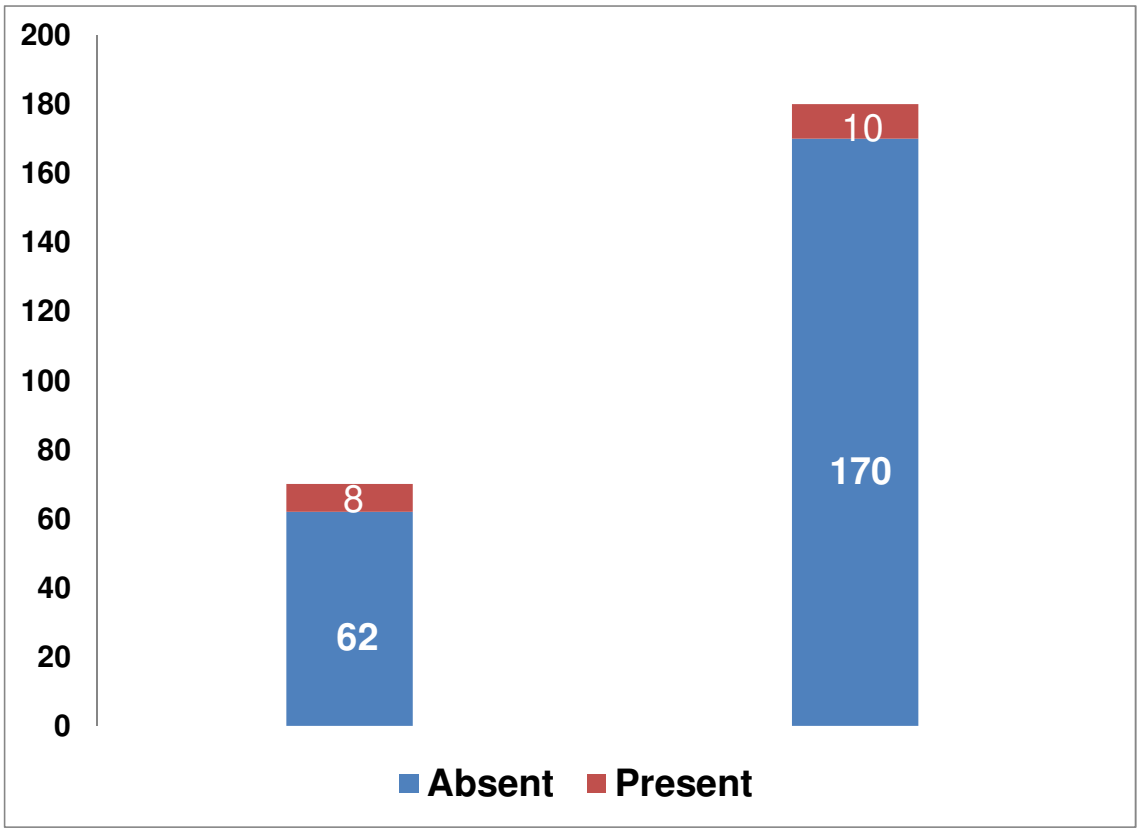

| | | | Carotid Disease | | |
|---|---|---|---|---|---|
| | | | Absent | Present | Total |
| CAD | No | Count | 221 | 3 | 224 |
| | | % within CAD | 98.7% | 1.3% | 100.0% |
| | Yes | Count | 11 | 15 | 26 |
| | | % within CAD | 42.3% | 57.7% | 100.0% |
| | Total | Count | 232 | 18 | 250 |
| | | % within CAD | 92.8% | 7.2% | 100.0% |

## DYSLIPIDEMIA & CAROTID DISEASE



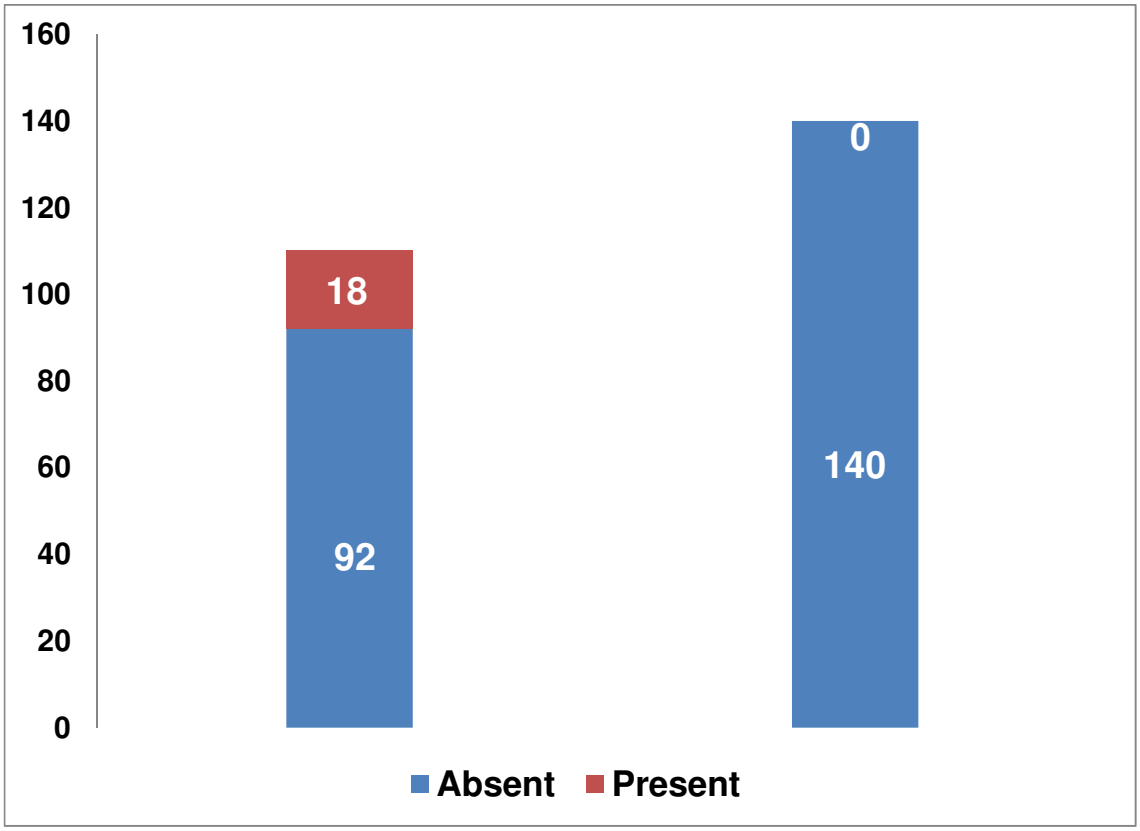

| | | | Carotid Disease | | |
|---|---|---|---|---|---|
| | | | Absent | Present | Total |
| DYSLIPIDEMIA | No | Count | 230 | 6 | 236 |
| | | % within DYSLIPIDEMIA | 97.5% | 2.5% | 100.0% |
| | Yes | Count | 2 | 12 | 14 |
| | | % within DYSLIPIDEMIA | 14.3% | 85.7% | 100.0% |
| | Total | Count | 232 | 18 | 250 |
| | | % within DYSLIPIDEMIA | 92.8% | 7.2% | 100.0% |

## SMOKING & CAROTID DISEASE




| | | | Carotid Disease | | |
|---|---|---|---|---|---|
| | | | Absent | Present | Total |
| SMOKER | No | Count | 62 | 8 | 70 |
| | | % within SMOKER | 80.0% | 20.0% | 100.0% |
| | Yes | Count | 170 | 10 | 180 |
| | | % within SMOKER | 95.2% | 4.8% | 100.0% |
| | Total | Count | 232 | 18 | 250 |
| | | % within SMOKER | 92.8% | 7.2% | 100.0% |

## ETIOLOGY & CAROTID DISEASE




| | | | Carotid disease | | |
|---|---|---|---|---|---|
| | | | Absent | Present | Total |
| ETIOLOGY | ASO | Count | 92 | 18 | 110 |
| | | % within ETIOLOGY | 83.6% | 16.4% | 100.0% |
| | NON ASO | Count | 140 | 0 | 140 |
| | | % within ETIOLOGY | 100.0% | .0% | 100.0% |
| | Total | Count | 232 | 18 | 250 |
| | | % within ETIOLOGY | 92.8% | 7.2% | 100.0% |

## ANALYSIS

Two hundred and fifty consecutive patients were studied over 1 year. The mean age of the patients was 50±20 years; there were 242 (96.8%) men and 8 (3.2%) women; 72% of the patients had a history of smoking, 10.4% had coronary artery disease, 5.6% had hypertension, 5.6 % had dyslipidemia and 17.2% had diabetes mellitus. Eighteen (7%) patients had carotid artery disease detected by carotid artery duplex scanning of which insignificant Carotid artery disease found in 10 patients,significant carotid artery stenosis in 5 patients and complete occlusion of ICA in 3 patients.

DIABETIC MELLITUS & CAROTID DISEASE

p value < 0.05

Risk Estimate

| | | 95% confidence interval | |
|---|---|---|---|
| | Value | Lower | Upper |
| Odds Ratio for DM | 9.821 | 3.547 | 27.195 |

HYPERTENSION & CAROTID DISEASE

p value < 0.05

Risk Estimate

| | | 95% confidence interval | |
|---|---|---|---|
| | Value | Lower | Upper |
| Odds Ratio for HT | 7.051 | 2.159 | 23.035 |

CAD & CAROTID DISEASE

p value < 0.05

Risk Estimate

| | | 95% confidence interval | |
|---|---|---|---|
| | Value | Lower | Upper |
| Odds Ratio for CAD | 100.4 | 25.28 | 399.12 |

Dyslipidemia & Carotid Disease

p value < 0.05

Risk Estimate

| | | 95% confidence interval | |
|---|---|---|---|
| | Value | Lower | Upper |
| Odds Ratio for Dyslipidemia | 230 | 41.92 | 1261.896 |

SMOKING & CAROTID DISEASE

p value < 0.05

Risk Estimate

| | | 95% confidence interval | |
|---|---|---|---|
| | Value | LOWER | UPPER |
| Odds Ratio for Smoker | 0.200 | 0.073 | 0.545 |

value < 0.05

Risk Estimate

| | | 95% confidence interval | |
|---|---|---|---|
| | Value | LOWER | UPPER |
| Odds Ratio for Etiology | 0.836 | 0.77 | 0.908 |

In this study patients with critical limb ischemia due to non-atherosclerotic disease were 56% and due to atherosclerotic disease were 44%.

In this study there is no prevalence of carotid disease in patients with critical limb ischemia due to non-atherosclerotic disease

The prevalence of asymptomatic carotid disease in critical limb ischemia patients is more common in elderly age group and in patients with DM,CAD and dyslipidemia ($p < 0.05$) which is statistically significant.

The asymptomatic carotid disease is more prevalent in patients with large vessel occlusion(Aorta,Iliac level occlusion) .

The asymptomatic carotid disease is present only in patients with atherosclerotic occlusive disease (16.4%) similar to other studies reported.

On multivariate analysis dyslipidemia, coronary artery disease and DM seemed to have independent influence ($p < 0.05$) which is statistically significant.

## CONCLUSION

The prevalence of asymptomatic carotid artery disease in Indian subgroup patients with critical limb ischemia is 7%. However this study demonstrates a relatively high prevalence of carotid artery disease in patients with peripheral arterial disease due to atherosclerotic occlusion is 16.4% ($p < 0.05$) which is statistically significant.

All patients with peripheral vascular disease with large vessel occlusion due atherosclerosis have to be screened for carotid artery disease.