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Iram Naz

Aga Khan University Hospital Karachi, Pakistan, iram.naz@aku.edu

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NOT ALL ASYMPTOMATIC CAROTID PLAQUES ARE EQUAL: SOME REQUIRE INTERVENTION

Dr. Iram Naz

Section of vascular surgery, Department of Surgery, Aga Khan University Hospital, Karachi, Pakistan

Correspondence to: Iram Naz, Department of Surgery, Aga Khan University Hospital, Karachi, Pakistan; iram.naz@aku.edu

ABSTRACT:

Ischemic stroke represents a major health hazard around the world, which has a severe impact on society and the health-care systems. Roughly, 15% of all strokes can be attributed to significant atherosclerotic disease of the carotid arteries. Some patients presenting with disabling strokes for the first time cannot benefit from carotid revascularization having lost the opportunity of prevention. We know that all symptomatic patients were once asymptomatic. Hence, after identifying high risk carotid plaques and patient's characteristics suitable for interventions, they should be offered carotid revascularization at specialized centers (with low perioperative stroke and death rates) to prevent stroke and cognitive function decline in long term.

INTRODUCTION:

Extra cranial carotid artery atherosclerosis is one potentially preventable risk factor for Stroke worldwide. The locations most frequently affected by carotid atherosclerosis are the proximal internal carotid artery (i.e., the origin) and the carotid bifurcation. Progression of atheromatous plaque at the carotid bifurcation results in luminal narrowing, often accompanied by ulceration. This process can lead to an ischemic stroke or transient ischemic attack (TIA) from embolization, thrombosis, or hemodynamic compromise. Asymptomatic patients are usually identified after auscultation of bruits or patients undergoing Coronary Artery Bypass Grafting (CABG) in our country, as routine screening for patients at high risk is not practiced here. Various risk factors, management options (best medical therapy(BMT), carotid interventions) have been studied in randomized trials around the world and international guidelines have been developed for intervention for symptomatic and asymptomatic carotid artery disease 1,2,3,4. All recent guidelines recommend considering Carotid endarterectomy (CEA) in patients with a 60-99% NASCET asymptomatic stenosis 5. All guidelines demand a low perioperative stroke and death rate (2-3%) 1, 2,3,4,5. The real question arises which asymptomatic plaques will benefit more from carotid revascularization. This review article aims to describe an approach to such asymptomatic patients and the challenges of management in Pakistan.

Treatment of asymptomatic Carotid Stenosis (ACS): Cons:

Some authors think that current risk of stroke in asymptomatic patients on best medical therapy is less than 1%, so >95% of the cases should be left untreated. 6, 7, 8 In addition, significant improvements in Best Medical Therapy (BMT) have occurred over time, especially lipid lowering drugs (used in only 10% of patients in the ACST trial and in 80% at 10-year follow-up) 9, 10. Addition of CAS to carotid revascularization has further confused the data as it has high perioperative stroke rate as compared to CEA¹¹.

Treatment of ACS: Pros

Repair of carotid stenosis, in addition to best medical therapy (BMT), is currently the best way to treat most asymptomatic patients with 60% to 99% carotid stenosis. Carotid stenosis causes preventable strokes. After a significant carotid stenosis has developed, that lesion remains a threat to the patient until it is removed. In the Asymptomatic Carotid Surgery Trial (ACST) 9 the annual risk of stroke after repair (0.55%) was much less than the annual risk with BMT alone (1.9%). The Asymptomatic Carotid Atherosclerosis Study (ACAS) 12 and ACST studies both compared carotid endarterectomy (CEA) plus BMT vs BMT alone, and both studies demonstrated a decreased risk of stroke by approximately 50% at 5 years, even though both studies were biased against repair^{9, 11}. In addition; some carotid plaque may not response to BMT as stroke risk is never zero in many trials worldwide.

Over time, there has been a standardization of technique for carotid endarterectomy by vascular surgeons resulting in reduced perioperative morbidity and mortality.

Perioperative stroke and death rate for CEA in asymptomatic patients have gone down from 3.1% in ACST trial⁹ to 1.1% in CREST trial. In the real world, surgeons must have such low incidence to offer CEA to asymptomatic patients.

The unfortunates who present with stroke due to carotid stenosis (and their even more unfortunate counterparts who experienced a fatal stroke as the first sign of trouble) all harbored an asymptomatic lesion before their respective events. Carotid repair used judiciously in concert with BMT and performed well can have life-long protective effects against stroke-related death and disability for patients with asymptomatic carotid stenosis^{9, 12, 13}. Vladimir¹⁴, Phil Gorelick¹⁵ and others¹⁶, have taught us that silent strokes become evident largely through cognitive decline. Once the great scientist in 1672, Thomas Willis said "Foolishness may also result from great Strokes". Also, the incidence of silent strokes may be as high as 9-fold as that of evident strokes¹⁷. These statistics are from the United States.

We don't know our statistics in Pakistan. Recently, Akiko Takaiwa¹⁸ demonstrates improvement of cognitive function in asymptomatic patients by revascularization. This was limited to a very small group of 15 patients.

The Role of Carotid Endarterectomy in ACS:

Guidelines on CEA for asymptomatic carotid stenosis are largely based on the result of 2 large, randomized studies of CEA versus BMT; ACAS, and ACST. The ACAS trial randomized 1662 adults (Ages 40 to 79 years) with 60-99% carotid stenosis. They followed up the patients at 2.7 years. The aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was estimated to be 5.15 for surgical patients and 11.0% for patients treated medically, an aggregate risk reduction of 53% (95 Confidence Interval, 22%-72%).

In the ACST, 3120 patients with over 60% mainly asymptomatic carotid stenosis were randomized to either immediate CEA plus medical treatment versus medical treatment alone or until the operation became necessary. ACST-1 reported 10 year stroke prevention, combining perioperative events and strokes. Net risks were 6.9% versus 10.95 at 5 years (gain 4-1%, 2.0-6.2) and 13.4% versus 17.9% at 10 years (gain 4.65, 1.2-7.9). They concluded that net benefit in future patients will depend on their risks from unoperated carotid lesions (which will be reduced by medication), or future surgical risks (which might differ from those in trials) and on whether life expectancy exceeds 10

years.¹⁰

Factors influencing benefit and risk:

A number of factors may influence the risk/benefit ratio with endarterectomy and thus decision to treat individual patients with asymptomatic carotid disease. The selection of asymptomatic patients should be guided by an assessment of co-morbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preference. Patients who are unlikely to benefit from CEA include those who have severe comorbidity due to other medical or surgical illness, patients with a prior ipsilateral stroke associated with persistent disabling neurologic deficits, and patients with total occlusion of the internal carotid artery.

1. Gender: The benefit of CEA appears to be greater for men than for women with asymptomatic carotid disease. (ACST)¹⁹.

2. Risk Stratification:

a) Asymptomatic embolism: Transcranial Doppler Ultrasound (TCD) is a non-invasive technique that can be used to detect circulating emboli. If clinical embolism is a good predictor of the subsequent risk, asymptomatic cerebral emboli might also predict clinical stroke risk²⁰. Recently, a large prospective and multi-center study (ACES, asymptomatic Carotid emboli study) evaluated the relationship between asymptomatic emboli and stroke risk in 467 patients with an ACS of at least 70%. The detection of emboli was associated with an increased risk for ipsilateral TIA and stroke (HR 2.54, 95% CI 1.2-5.36) and in particular for ipsilateral stroke (HR 5.57, 95% CI 1.61-19.32) during 2 years of follow-up even after adjusting for antiplatelet therapy, degree of stenosis, and other risk factors.

b) Carotid plaque morphology: Carotid plaque echolucency measurement by grey scale Measurement²¹ and recently, data from ACES demonstrated that plaque morphology assessed using a simple visual rating scale predicts ipsilateral stroke in ACS²². 435 patients with ACS $\geq 70\%$ were included and followed-up for 2 years. Plaque echolucency at baseline was associated with an increased risk of ipsilateral stroke alone (HR 6.43, 95% CI 1.36-30.44). A combination of plaque echolucency and ES positivity was associated with

increased risk of ipsilateral stroke alone (HR 10.61, 95% CI 2.98-37.820). The combination of ES detection and plaque morphology allows a greater prediction and identifies a high risk group with an annual stroke risk of 8%, and a lower risk group with a risk of <1% per year.²²

c) **Magnetic Resonance Imaging (MRI) of plaque:**

MRI is a non-invasive method of plaque measurement that does not involve ionizing radiation. Initial result from a prospective study demonstrated an increased risk of ipsilateral cerebrovascular events has also been reported over a mean follow-up period of 38.2 months in asymptomatic patients who had 50-79% stenosis and the presence of a thin or ruptured fibrous cap, intraplaque hemorrhage, or a larger lipid rich necrotic core.²³

3. Stroke heterogeneity: Strokes occurring in the territory of an ACS are not always caused by carotid lesion. Indeed, data from NASCET 5 show that almost 50% of the strokes in the territory of a greater than 60% ACS are due to small vessel disease ("lacunar") and cardio embolic disease.²⁴

4. Contra lateral carotid artery stenosis or occlusion: The findings on this are conflicting in literature. Mostly Authors suggest no benefit of intervention in high grade stenosis with contra lateral occlusion.²⁵

5. Degree of stenosis:

Neurologically asymptomatic patients with >60% NASCET stenosis, should be considered for CEA provided the patient has a 3-5 year life expectancy and peri-operative stroke/death rates of 3% or less.³

Coronary arteries bypass grafting (CABG) Surgery in the presence of asymptomatic high grade carotid stenosis:

Studies suggest that previous or simultaneous CEA in patients with unilateral severe asymptomatic carotid stenosis undergoing CABG could prevent stroke better than delayed CEA, without increasing the overall surgical risk.^{26, 27, 28}

Role of Carotid stenting in Asymptomatic Carotid stenosis:

There is no data at present to support the preferential use of CAS over CEA in asymptomatic patients that are

good surgical candidates. Neither SAPHIRE nor CREST29 trials address the question now posed by improvement in BMT, namely whether patients with ACS should undergo any revascularization procedure. The Transatlantic asymptomatic carotid intervention trial will investigate current BMT in combination with CEA or CAS compared with BMT alone in patients with asymptomatic carotid disease³⁰. Few other trials are currently in progress including SPACE 2 study.

Current status of Stroke and stroke care in Pakistan:

No large scale epidemiological studies are available to determine the true incidence of stroke in Pakistan. Estimated annual incidence is 250/100,000, translating to 350,000 new cases every year. Stroke related mortality in the acute stage has been reported in the range of 11-30%³¹. Large artery atherosclerosis accounted for 26.9% of all stroke in 393 patients presenting with stroke, less than lacunar subtype from the Aga Khan University Stroke data bank³². Few studies reported on carotid diseases, ranged from 7-19%^{33, 34}, but these were among patients presented with neurological events so were not asymptomatic patients. A study from Pakistan reported low frequency of carotid atheromatous disease in patients with recent stroke or TIA³⁵. They performed carotid Doppler at two centers. Potentially surgically correctable disease, defined as 70-99% carotid artery stenosis was present in only 79/672(12%) cases. Only 4 (0.5%) underwent intervention meaning a low utilization of procedures. Various factors were discussed for this underutilization. These included lack of awareness about prevention of stroke by intervention, on part of the physician or the physicians may have considered those patients not candidates for surgery. Other factors include self pay status of many middle and poor class patients and significant price variation for health care (physician fee, diagnostic work up and hospitalization) as compared to developed countries. There are very few studies on safety of carotid endarterectomy in Pakistan. During a 10 year period, 59 patients underwent carotid endarterectomy at single center by single vascular surgeon, 11 of which underwent simultaneous coronary artery bypass grafting (CABG). Mortality was 27% in patients undergoing CEA and CABG versus 2% undergoing CEA alone³⁶.

An Audit in 2012 (unpublished data) showed increased number of CEA from the same center. 157 patients undergoing CEA between 1990 and Feb 2012 were included (59 patients of previously published study³⁶ are included). There were 123 Males. 34 patients had

simultaneous CEA and CABG. Perioperative stroke rate was 3.1% in carotid endarterectomy alone and 5.1% in combined CEA and CABG group.

Two centers have published results of carotid stenting in Pakistan^{37, 38}. They were performed for various indications, in high risk group, mostly unfit for surgical intervention.

How to approach Asymptomatic Carotid stenosis patient in 2013?

Any patient diagnosed to have a bruit on clinical examination or found to have high grade stenosis >70% on carotid Doppler ultrasound, should be evaluated further for identifying vulnerable plaques by TCD, echolucency and ulceration on ultrasound, MRI of plaque, or biomarkers when available. Based on individual characteristics e.g. life expectancy with availability of centers with low perioperative stroke/death rate of <3% of CEA, patients should be counseled about risk reduction by CEA. High risk candidates can be offered CAS, if risk of stroke is very high.¹

Future of Stroke prevention in Pakistan:

Public Awareness to sensitize masses about stroke prevention is urgently needed in Pakistan. World Health Organization (WHO) recommends a stepwise approach (STEPS Stroke) through the use of standardized tools and methods for ongoing core, expanded, and optional data collection. The main principle of this approach is a phased implementation of interventions-core, expanded and optimal-based on the availability of resources and political and community support³⁹. In addition to vascular risk factor modification, studies should be carried out in asymptomatic high vascular risk groups (survivors of coronary and peripheral artery diseases) to determine prevalence of frequency of vulnerable plaque in carotid arteries as done in west. Till then high cost mass screening would not be a cost effective option especially in a politically volatile situation in Pakistan.

We have no level I data showing that BMT alone in any era has been better than BMT plus repair⁴⁰. Also given that there will be noncompliance and intolerance in real world (that reduce the efficacy of the medical regimen); relying on BMT alone as compared to otherwise safe intervention⁴¹ seems illogical. In addition to the disadvantages of BMT, there is a downside to lack of repair: continued annual risk of stroke in excess of the annual risk after repair, psychological effects of living

with a threatening lesion, and the potential of long-term cognitive deterioration.

We as a scientific community should strive to create new knowledge about management of asymptomatic carotid stenosis in developing countries as we cannot afford high cost screening and stroke care as offered in Europe and North America. Till then, we have to use their data and individualize care of our patients.

CONCLUSIONS:

Until we get epidemiological data on frequency and outcome of carotid artery disease in Pakistan, we cannot deprive our high stroke risk patients from carotid interventions. There is a need for more collaboration with neurologist community for early referrals. And emphasis for an international stroke nongovernmental organization to reach a consensus on comprehensive stroke prevention strategies in south Asia. Till then, we should continue to provide carotid repair to good-risk patients with significant asymptomatic carotid stenosis and continue to look for ways to identify patients most likely to benefit from repair.

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