

# Frequency and Outcome of Carotid Atheromatous Disease in Patients With Stroke in Pakistan

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**Background and Purpose**—Limited data exist on the frequency and outcome of carotid artery disease in Pakistan. Such information would help guide the usefulness of screening for the condition in this low-middle income health care setting.

**Methods**—A prospective, descriptive study was conducted among 3 large teaching hospitals in Karachi, Pakistan. Patients referred for carotid Doppler ultrasound examination were included if they had experienced a stroke or TIA within the previous month. The severity and morphology of carotid disease were characterized by trained technicians using standardized criteria. Demographic and risk factor data were collected at baseline, and the outcome of patients was assessed at least 6 months later.

**Results**—A total of 672 patients underwent bilateral carotid Doppler ultrasound (1344 carotid examinations). The findings revealed 0% to 50% stenosis in 526 (78%), 51% to 69% stenosis in 57 (8%), 70% to 99% stenosis in 82 (12%), and total occlusion in 7 patients (1%). Potentially surgically correctable disease, defined as 70% to 99% carotid artery stenosis, was present in only 79 (12%) patients, of whom 47 (60%) were ipsilateral symptomatic, 15 (20%) asymptomatic, and 17 (20%) had status unknown. Outcome information at  $\geq 6$  months follow-up was available for 36 of the 47 (76%) surgically correctable and only 4 of these patients (12%) had undergone surgical or radiological intervention (carotid endarterectomy in 3 patients and carotid stenting in 1 patient).

**Conclusion**—The frequency of carotid artery disease of at least moderate severity is very low in patients with recent stroke or TIA and there is low utilization of high-cost, carotid intervention procedures in Pakistan. These data raise questions regarding the applicability and cost-effectiveness of routine carotid ultrasound screening in our country and similar population in Asia. The local socio-economic and clinical data do not support routine carotid Doppler ultrasound in every patient with stroke and TIA in Pakistan. Studies are warranted to determine predictors of significant carotid artery stenosis in stroke/TIA patients of our country to develop reliable stroke guidelines appropriate for local population. (*Stroke*. 2009;40:708-712.)

**Key Words:** carotid ■ Doppler ■ stroke

Extracranial carotid artery atheromatous disease, most frequently occurring at the bifurcation and proximal segments of the internal carotid artery, is a leading cause of ischemic stroke, accounting for up to 40% of such events in Western countries.<sup>1</sup> Studies have reported racial differences in the severity and distribution of carotid atherosclerosis.<sup>2</sup> Previous studies indicate that people of South Asian origin have higher rates of cardiovascular disease and stroke than people of European origin, a finding that cannot be explained entirely by differences in conventional cardiovascular risk factors, such as smoking, elevated blood pressure, diabetes, or raised serum cholesterol.<sup>3,4</sup>

On the basis of randomized evidence indicating benefit of carotid endarterectomy/stenting in patients with  $>70\%$

symptomatic carotid stenosis,<sup>5-7</sup> current stroke guidelines recommend use of carotid Doppler ultrasonography in all patients with recent stroke or TIA.<sup>8,9</sup> However, there is uncertainty about the applicability of such guidelines to developing countries where the frequency of carotid disease and expertise in intervention is much lower.<sup>10</sup> Racial differences in the distribution of extracranial and cerebral vascular occlusive disease are well-documented.<sup>11-18</sup> Bauer et al<sup>19</sup> first suggested racial differences in the distribution of cerebral atherosclerosis in an angiographic study of patients admitted to a single hospital. The amount of carotid atherosclerosis seen among South Asians is much lower even after adjustment for age, sex, and recruiting center.<sup>20-21</sup>

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The data regarding frequency of carotid artery disease in Pakistan are limited. One hospital-based study showed a frequency of 13% “high-grade” carotid stenosis in patients with ischemic stroke.<sup>22</sup> The aim of our study was to evaluate the frequency of carotid disease in patients with recent stroke or TIA, and to determine those factors associated with carotid stenosis in the population of Pakistan. We also examined the outcome of carotid Doppler ultrasound in relation to guidelines recommended for symptomatic patients with high-grade stenosis and made some estimates of the cost-effectiveness of carotid Doppler ultrasound in the management of stroke.

## Materials and Methods

A prospective multi-center descriptive study was conducted at the Aga Khan University, Ziauddin Medical University, and Advanced Radiology Centre in Karachi, Pakistan from August 2005 to October 2006.

Aga Khan University and Ziauddin Medical University are major tertiary care facilities in the private sector, situated in a provincial capital and most populous city (Karachi) of the country (Pakistan). These 2 facilities mostly see patients from upper-middle class or upper-class income groups. Most patients undergoing carotid Doppler ultrasound at these facilities are inpatients with diagnosis of stroke or TIA. The city has a population of  $\approx 10$  million, and the city attracts people across the country to seek medical advice, in addition to employment and business. In the province of Sindh, almost all of the trained neurologists are practicing in Karachi, so catchment area for neurological disorders is the whole province. Advanced Radiology Centre is an important diagnostic facility for radiological procedures in the private sector and its catchment area is mainly Karachi city. This facility mostly caters to lower-class and upper-middle class patients. All patients coming to this facility are referred from family physicians, internists, and neurologists. There are  $>22$  facilities in Karachi providing carotid Doppler ultrasound examinations. We could not obtain the data regarding how many examinations are performed at these facilities over the course of 1 year. Estimated incidence of stroke in Karachi is  $\approx 15\ 000$  to  $20\ 000$  per year. If we assume that 30% to 50% patients were able to afford carotid Doppler ultrasound examination, then an estimated 5000 to 7000 examinations are probably performed. We were able to obtain information for  $\approx 10\%$  of these patients.

All patients aged 18 years or older who were referred for carotid Doppler were enrolled if they had a diagnosis of stroke or TIA within the previous month. Patients with cerebral contusions, intracerebral, subarachnoid, subdural, and epidural hemorrhage were excluded.

The history of potential vascular risk factors associated with carotid atherosclerosis was obtained from each patient and from the medical records. A diagnosis of hypertension was made if the patient's blood pressure was  $>140$  (systolic) or  $>90$  (diastolic) mm Hg on repeated measurements during hospitalization or physical evaluation, or if the patient was being treated with antihypertensive drugs. A diagnosis of diabetes mellitus was based on clinical assessment, fasting serum glucose level, or if the patient was being treated with insulin or hypoglycemic drugs. History of cigarette smoking was positive if the patient had smoked  $\geq 10$  cigarettes daily for  $>10$  years. Medical management of stroke prevention included control of diabetes mellitus, control of hypertension, smoking cessation, at least 1 antiplatelet agent and statins.

## Ultrasonography

Carotid ultrasound was performed during the baseline clinic visit under the supervision of a trained radiologist. At Ziauddin Medical University Hospital, Karachi, Toshiba Power vision 6000 (multi-frequency 7.5–11 MHz probe set to 7.5 MHz) was used, whereas at Advanced Radiology Center, Karachi, the carotid Doppler was performed on POWER VISION 6000 by TOSHIBA using a multi-frequency linear probe (7.5–11 MHz). At the Aga Khan University Hospital, Karachi, GE Logic 500 (7.5-MHz probe) and Aloka SSD

4500 (7.5-MHz probe) were used. In 672 patients, 1344 carotid Doppler examinations were performed.

All internal carotid artery (ICA) examinations were performed with grayscale, color Doppler, and spectral Doppler ultrasound. The degree of stenosis determined at grayscale and Doppler ultrasound was stratified into the categories of normal (no stenosis),  $<50\%$  stenosis, 50% to 69% stenosis,  $\geq 70\%$  stenosis to near occlusion (99%), and total occlusion. ICA peak systolic velocity and the presence of plaque on grayscale or color Doppler images were primarily used in the diagnosis and grading of ICA stenosis. ICA was diagnosed as normal when ICA peak systolic velocity was  $<125$  cm/sec and no plaque or intimal thickening was visible,  $<50\%$  stenosis when ICA peak systolic velocity was  $<125$  cm/sec and plaque or intimal thickening was visible, 50% to 69% stenosis when ICA peak systolic velocity was 125 to 230 cm/sec and plaque was visible,  $\geq 70\%$  stenosis to near occlusion when ICA peak systolic velocity is  $>230$  cm/sec and visible plaque and lumen narrowing were seen, near occlusion when there was a markedly narrowed lumen on color Doppler ultrasound, and total occlusion when there was no detectable patent lumen on grayscale US and no flow on spectral, power, and color Doppler ultrasound.<sup>23</sup>

## Follow-Up

Follow-up was information was collected by a physician by telephone interviews or direct interview at the time of clinic visit. The duration of follow-up (time since date of procedure) was 7 months to 21 months (average, 13 months). Follow-up data were obtained only for patients with ipsilateral, symptomatic, high-grade (70% to 99%) stenosis ( $n=47$ ). Follow-up information collected from these patients was related to surgical or endovascular intervention (whether it was offered, whether surgery or stenting was performed, and the reasons for not undergoing the intervention). The reasons for not undergoing intervention was an open-ended question and responses to these questions are provided in Table 2. The data regarding additional or follow-up scans were not collected.

## Statistical Analyses

Data analysis was performed using SPSS version 13.0. Continuous variables were expressed as mean  $\pm$  SD. Two-sided unpaired *t* test was performed for continuous variables and  $\chi^2$  test (or Fisher exact test when appropriate) for discrete variables. Multivariate stepwise logistic regression analysis was performed to detect independent predictors of carotid artery disease using factors that had significant relation in univariate analysis. A value of  $P<0.05$  was considered statistically significant.

## Results

A total of 672 patients underwent bilateral carotid doppler ultrasound (1344 carotid Doppler examinations). Demographic data and findings of carotid Doppler studies are detailed in Table 1.

Six months or more of follow-up was available for 36 of 47 (76%) surgically correctable symptomatic patients (mean, 12 months; range 6–18 months). Details of the follow-up are reported in Table 2.

Out of 672 patients with stroke or TIA, only 79 (12%) had surgically correctable carotid artery disease (70% to 99% stenosis), out of which only 4 (0.5%) underwent any intervention. The cost of carotid Doppler ultrasound with interpretation is on average equivalent to \$30 US. The total expenditure for carotid evaluation was \$20 160 US; 168 carotid Doppler ultrasound studies were performed (\$5040 US spent) for screening patients for 1 intervention (surgery or stenting). Per capita annual income for Pakistan is \$672 US.

**Table 1. Demographics, Vascular Risk Factors, and Carotid Doppler Ultrasound Findings\***

Demographics	(%)
Men	408 (61)
Women	264 (39)
Age, yr	Mean, 51; range, 22–89
Indication of study	
Stroke	591 (88)
TIA	81 (12)
Vascular risk factors	
Hypertension	392 (59)
Diabetes mellitus	249 (37)
Smoking	168 (25)
Carotid Doppler findings	
0%–50% stenosis	526 (78)
51%–69% stenosis	57 (8)
70%–99% stenosis	79 (12)
Total occlusion	10 (1)
Intimal thickening	141 (21)
Calcification	108 (16)
Plaque	106 (16)
Ruptured plaque	14 (2)
Ulceration	15 (2)
Thrombus	5 (1)

\*Percentages are rounded.

## Discussion

To our knowledge, this study is the largest multi-center study of stroke and TIA patients from Pakistan. Our findings are in agreement with previous reports of low frequency of carotid artery disease among Southeast Asian patients with stroke. The relations we found between carotid atherosclerosis and risk factors such as hypertension, smoking status, diabetes, major ECG abnormality, and the presence of carotid bruits were similar to those previously described.<sup>24–26</sup>

The frequency of substantial degree of carotid disease among patients with stroke and TIA is as low as asymptomatic population in United States. Examination of 1189 members of the Framingham cohort (asymptomatic), aged 66 to 93 years, revealed no disease in 30%, <50% stenosis in 62%, 50% to 74% stenosis in 5%, 75% to 99% stenosis in 2%, and 100% stenosis in 1%.<sup>27</sup> This distribution is comparable to the data of 672 patients with stroke or TIA in our study (symptomatic patients).

We identified various factors responsible for not undergoing best available treatment for high-grade stenosis among our patients. Fifteen percent of patients were not aware that surgical option was a valid available option for their disease. This could be attributable to lack of awareness on part of physician or the physician may have considered those patients not candidates for surgery and did not offer them surgical option. Carotid stenting is offered at only 1 center in Pakistan. The data regarding safety of carotid endarterectomy are limited from Pakistan. During a 10-year period, 59 patients underwent carotid endarterectomy, 11 of which

**Table 2. Surgically Correctable Disease**

Clinical status	(%)
Symptomatic	47 (60)
Asymptomatic	15 (20)
Not known	17 (20)
Follow-up ( $\geq$ 6 mo)	36 (76)
Therapy	
Interventional management	4/36 (12)*
Medical management	32/36 (88)
Reasons for not getting intervention	
Financial	12/32 (38)
High risk of complications	9/32 (25)
Intervention was not offered	5/32 (14)
Tried alternative therapy	3/32 (8)
No specific reasons	3/32 (8)
Vascular outcome	
Stroke†	1
TIA†	1
Total occlusion‡	3

\*Three underwent carotid endarterectomy and 1 underwent stenting.

†This patient was in a medically treated group.

‡None of these had stroke during follow-up.

Surgically correctable disease indicates 70%–99% stenosis; N=79.

underwent simultaneous coronary artery bypass grafting. Mortality was 27% in patients undergoing simultaneous carotid endarterectomy and coronary artery bypass grafting vs 2% undergoing carotid endarterectomy alone.<sup>28</sup> Most people we interviewed either cannot afford or are not willing to undergo carotid endarterectomy.

Despite being multi-center with the largest number of stroke and TIA patients from Pakistan, these results cannot be generalized. Large, prospective, multi-center studies are needed to evaluate the prevalence and predictors of carotid disease among Pakistani patients to develop reliable and cost-effective stroke guidelines appropriate for our population.

There are certain limitations to our study. Doppler studies are operator-dependent, with a sensitivity and specificity of 90% and 88%.<sup>29</sup> We did not analyze intraobserver or interobserver variability for evaluation of degree of stenosis, which may be a source of potential bias. We do not have the follow-up data available for 24% patients.

The data related to cost-effectiveness of screening carotid Doppler ultrasound for primary and secondary stroke prevention is reported from the US and Europe.<sup>30–33</sup> There are many well-documented grounds, limiting the generalizability and transferability of cost-effectiveness results beyond the geographical boundaries, even from 1 developed country to another.<sup>34,35</sup> Adopting these recommendation and guidelines to Pakistan will be rather more challenging.

First, there is a significant difference in basic demography and epidemiological profile of Pakistan and countries of Europe and America; for example, in 2006 gross national income per capita in Pakistan was \$800 US compared with high-income organization of economic cooperation for devel-



oped countries with an average income per capita of \$38 190 US. Similarly, life expectancy at birth in Pakistan is 65 years in comparison to 80 years in organization of economic cooperation for developed countries.<sup>36</sup> More importantly, morbidity and mortality data in both settings differ significantly.

Second, the health care system in Pakistan is in sharp contrast to that of developed countries of Europe and US, eg, physician density in Pakistan is 8 per 10 000 population, whereas in high-income countries it is 28, nurse density is 1 per 10 000 population, whereas in high-income countries it is 87, hospital beds per 10 000 population in Pakistan is 12 compared to high-income countries' average of 59.<sup>37</sup> Third, the health care financing patterns including the composition of health spending and providers' incentives are also dissimilar. Health care financing in Europe and US differs in volume (12% of gross domestic product) in high-income organization of economic cooperation for developed countries and 2% in Pakistan during 2005), and also in mode of finance for health care, ie, in Pakistan 82% of total spending on health care is privately financed, compared to organization of economic cooperation for developed countries with an average of 26%. More prominently, almost all private spending on health care in Pakistan is out-of-pocket (98%), whereas in high-income countries average out-of-pocket expenditure on health is 36% of total health expenditure.<sup>37</sup> This means that there is barely any type of third-party payment system in Pakistan. However, providers' incentives systems in Pakistan is a mix of salary and fee for service, usually provided by physicians in private practice.<sup>38</sup> Fourth, there is a significant price variation of different inputs (physician fee, medicine and diagnostics, hospitalization) for health care in Pakistan compared to organization of economic cooperation for developed countries and even within developed countries.<sup>39</sup>

All of these factor contribute to variation in the costs and effectiveness of treatment and diagnostics strategies across the regions and countries, eg, health expenditure in absolute terms is low, reflecting low ability to pay for health care by not only the government but also, more importantly, by private households. As such, based on our study results, we are not able to recommend generalizing the results of our study; however, we can advocate that American Heart Association guidelines for stroke management are not a sound evidence for practice in Pakistan for the reasons mentioned. More robust evidence on cost-effectiveness and clinical practice for prevention of primary and secondary stroke is needed to best-utilize already meager resources in terms of finance and delivery of health care, as well as health-seeking behavior in the country.

We found just 1 published study<sup>40</sup> on only the cost of acute stroke care in Pakistan in a private sector tertiary care hospital, without any data on effectiveness. Average cost per hospital discharge was ≈71 000 rupees (\$1179 US). Hospital bed/room fees accounted for 39% of total expenditure, followed by 19%, 18%, and 12%, respectively, for pharmacy, radiology, and laboratory charges.<sup>40</sup>

In a country where >40% of the population<sup>41</sup> is borne to catastrophic expenditure on health, along with least spending on health (<1 of gross domestic product),<sup>42</sup> 168 carotid Doppler examinations performed to identify 1 patient who is willing to

and can afford to undergo carotid endarterectomy or stenting cannot be predicted to be an economically viable strategy. Our observations illustrate that application of general guidelines should always be intelligently supported and, if required, adapted by local socio-economic and clinical data.

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## Disclosures

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