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The Benefit of Ultrasound Screening of Asymptomatic Carotid Stenosis in Diabetic Patients with Coronary Artery Disease

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Abstract

Background: The preventive task force reaffirmed its 2007 recommendation against screening for asymptomatic carotid stenosis with Doppler ultrasound (US). This recommendation was not tailored to include high risk subgroups (diabetics with coronary artery disease).

Methods: We conducted a retrospective case control study on previously asymptomatic, elderly, diabetic patients with history of coronary artery disease, who presented to our facilities between 2003 and 2009. Participants who had an US preformed were compared to controls who never had an US performed before. After five year period, we recorded outcomes of stroke, mortality and carotid endarterectomy.

Results: 316 patients were included (192 in study group, 124 controls). No difference in baseline characteristics was reported.18% of the study patients had 60% stenosis or more. The cumulative stroke incidence was similar between both groups (4.6% vs 2.4%), p>0.3. Two carotid artery endarterectomies were performed in the screened group. After adjusting for propensity scores, there was no association between stroke occurrence and ultrasound screening. The odds ratio for development of stroke was 0.2 (95% CI, 0.03-1.6, p=0.14) in unscreened group compared to screened group.

Conclusion: High atherosclerotic burden in this subgroup might lead clinicians to consider carotid US as a screening tool for stroke prevention. This study is the first to suggest that US does not prevent strokes in high risk subgroups. Large randomized studies are needed to confirm these results.

Keywords: Carotid stenosis; Ultrasound; Coronary artery disease; Diabetes; Stroke

Introduction

Stroke is a major public health issue with estimated 700,000 events reported annually in the United States. Little can be done to reverse the devastating effects of brain injury aside from rehabilitative interventions for the majority who go on to have a completed stroke. For this reason, the greatest impact on this disease comes from prevention.

Patients who have had a stroke or transient ischemic attack (TIA) due to carotid stenosis are considered symptomatic and often benefit from early carotid revascularization if the stroke is related to a high-grade stenosis of the extracranial carotid artery [1]. 80% of strokes occur in asymptomatic individuals, and forms of screening these individuals have not been cost effective. The preventive task force recently reaffirmed its 2007 recommendation against screening for asymptomatic carotid stenosis with Doppler ultrasound (US) [2]. This recommendation was based on studies not specifically tailored to include specific high risk subgroups, such as diabetic patients with coronary artery disease.

Patients with pre-existing cardiovascular disease and risk factors for further developing vascular disease are perceived as having a greater likelihood of developing carotid artery atherosclerosis and subsequently stroke by gradual progression of stenosis and embolization. Such high risk patients might still benefit from such preventive measure if studied separately.

Vascular disease progression is known to have a strong correlation with diabetes, smoking, hypertension. The prevalence of clinically important asymptomatic carotid stenosis 1% in the general population and >1% in those >65. It increases with age to reach 7.5% in those >80 years [3]. Carotid stenosis is defined as the atherosclerotic narrowing of the proximal internal carotid artery (>70% severe stenosis and >50% moderate stenosis). Emphasizing the importance of screening individuals with carotid stenosis and identifying high-risk groups for development of stroke would prove fruitful in terms of narrowing our scope to provide screening tests that may matter.

Methods

We conducted a retrospective case control study to evaluate the role of screening carotid (US) in asymptomatic, elderly, diabetic patients with history of coronary artery disease. The Study was conducted at North Shore LIJ Staten Island University Hospital and the Protocol was approved by the IRB of the institution. Informed consent was not required. Data on patient history, cardiac risk factors, co-morbid conditions vascular history, vital signs and laboratory tests were obtained retrospectively. Patients with missing data on important baseline clinical covariates were excluded from the sample. Charts and brain imaging reports were reviewed until 2014 for the occurrence of stroke and transient ischemic attack. The study group included patients who underwent carotid (US) between 2000-2009 for reasons other than stroke with documented history of coronary artery disease

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and Diabetes. Patients with documented history of stroke prior to the Carotid (US) were excluded. Indications for performing Carotid (US) included presence of carotid bruit on physical exam, screening prior to coronary artery bypass grafting and presence of risk factors for carotid artery stenosis at the discretion of multiple cardiologists within the hospital. The carotid (US) was performed in inpatient and outpatient setting of a single community center.

In order to select the control group, all records that had a dual ICD coding for diabetes and coronary artery disease between 2000 and 2009 were reviewed. We excluded those who had carotid (US) for any reason.

The following were used as exclusion criteria in both groups: age younger than 60 years old, concomitant or previous stroke/Transient ischemic attack, no history of Diabetes or established coronary artery disease.

Stroke was defined as neurologic deficit of cerebrovascular cause as evidenced by clinical presentation or correlated CT brain imaging that lasted for >24 hours. Transient ischemic attack was defined as a neurologic deficit that resolved completely within 24 hours. Asymptomatic carotid artery stenosis was defined as atherosclerotic narrowing of the lumen of the carotid bifurcation or the extracranial part of the internal carotid arteries of 60-99% without ipsilateral carotid territory symptoms. Nonspecific symptoms such as syncope or dizziness are not considered symptomatic. Duplex Ultrasound was the method of screening used. A degree of stenosis more than 60% by US was considered clinically significant. Diabetes was defined by the presence of HbA1c >5.7% or by documented antiglycemic medications. Coronary artery disease was described as evidence of obstructive or non-obstructive lesions on coronary angiogram.

Statistical Analysis

Since our data was nonrandomized, we used propensity scores to estimate the effect of ultrasound screening on stroke prevention. The sample was restricted to those patients who had concurrent diabetes and coronary artery disease documented in the chart. An initial propensity score model was estimated using the variables collected. To estimate the propensity score, a logistic regression model was used in which screening status (receipt of a carotid ultrasound test vs no ultrasound performed) was regressed on the baseline characteristics. In the overall sample, continuous variables and categorical variables were compared between screening groups using the standard t test and chi-square or Fisher tests, respectively. The association of stroke and ultrasound was examined adjusting for the previously-calculated propensity score. The variables that can affect the outcome stroke were included in the model. Screened and unscreened participants were matched 1:1 on the propensity score. Overlap of scores was checked and in the event of the resulting partial overlap, 176 patients were excluded. The score included those variables that were associated with both ultrasound and stroke. Those who were excluded had the highest and lowest score. Statistical analyses were conducted using Stata version 9.3 (Stata Corp, College State, Texas).

Results

Among 5440 charts that were reviewed, only patients who were older than 60 years, had diabetes and established coronary artery disease were included (Figure 1). The final sample size was 316 patients. 52% were men and mean age was 73 ± 12. Sixty percent (N=192) had undergone ultrasound screening at the discretion of the ordering physician. Forty percent (N=124) did not have an ultrasound performed at the time they were included in the study. All patients were followed up for at least 7 years. In both groups, participants were at least on one type of antiplatelet medication as well as a statin during the follow up period. Among 192 patients in the study group, 184 had evidence of carotid stenosis ≥ 39% by US. 96% had bilateral carotid disease. Only 18% of those screened had a degree of stenosis ≥60%. Two carotid artery endarterectomies were performed in the screened group and none in the control group. Vascular interventions were performed in those two cases after the progression of the initial mild stenosis found on ultrasound at the time of inclusion to a degree of stenosis >70%. The cumulative stroke incidence was similar between the screened and unscreened group, (4.6% vs 2.4%, and p>0.3, respectively). All-cause mortality was (12.5% vs 17%, p=0.87). The two groups differed significantly in demographic, medical and treatment characteristics (Table 1).

Since the groups were not randomized, we adjusted for the bias of referral by using propensity score matching. Only variables that were significantly associated with both outcome and ultrasound screening were included in the propensity scores (Table 3). Propensity scores of both groups partially overlapped. In the screened group the maximum, minimum and mean scores were 0.91, 0.12 and 0.71, respectively. In the unscreened group, the maximum, minimum and mean scores were 0.91, 0.08 and 0.47, respectively. Both the analysis of the entire sample and the analysis of the remaining sample (N=184) after exclusion of outlying propensity scores were performed. Results were similar for both analyses: none of the variables represented a significant risk for the occurrence of stroke. In addition, there was no association between stroke occurrence and ultrasound screening. The odds ratio for the incidence of stroke was 0.2 (95% CI, 0.03-1.6, p=0.14) in those who were not screened compared to those who were. In the subgroup analysis that compared patients with different coronary artery disease therapy (medical vs percutaneous vs surgical), screening with ultrasound did not have a preventive effect p=0.8. Participants who developed stroke (N=12) had a clinically significant stenosis of >60% in three cases while two events occurred in the unscreened group. Among those who had a cerebrovascular event, seven patients had a luminal narrowing of <39% at the time of inclusion into the study. None of the cerebrovascular

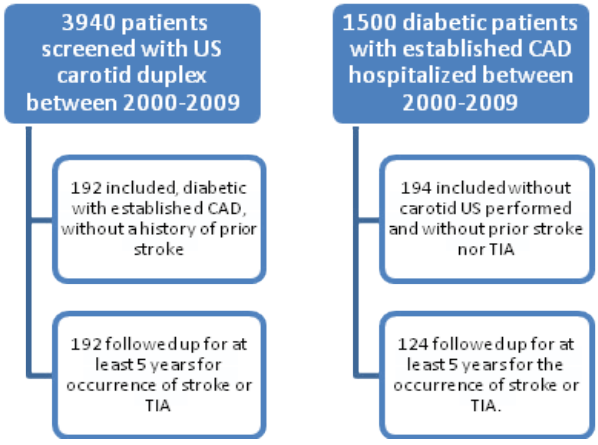


Figure 1: Study design. Representation of the study flow, CAD: Coronary Artery Disease TIA: Transient Ischemic Attack, US: Ultrasound.

Characteristics %	Screened Group N=192	Non Screened Group N=124	Total group N=316	p value
Age	75 ± 11	71 ± 13	73 ± 12	0.006
Male gender	52	52	52	0.09
Smoking	70	36	58	<0.001
DM2	98	50	79	<0.0001
IDDM	2	50	21	
HTN	83	94	88	<0.002
CAD (PCI)	23	22.5	22.7	<0.0001
CAD (CABG)	29	42	34	
Absence of Aortic Stenosis	82	90	84	<0.0001
CKD	14	26	19	<0.002
Atrial fibrillation	17	20	18	<0.007
ACE inhibitor	44	59	50	<0.002
Beta blockers	62	72	66	<0.02
Calcium blocker	26	30	28	0.07
Aspirin	74	61	69	<0.0001
Dual antiplatelet	1.6	11	5	
Statin	80	81	81	0.08
Ejection Fraction<60%	11	21	15	0.009

Table 1: Characteristics and demographical variables. Univariate analysis of results in both groups. CABG: Coronary Artery Bypass Graft, CAD: Coronary Artery Disease, CKD: Chronic Kidney Disease, DM2: Diabetes Mellitus 2, IDDM: Insulin Dependent Diabetes Mellitus.

Outcomes	Screened group %	Non screened	Population	p value
Stenosis > 60%	18	N/A		
Stroke	4.6	2.4	3.8	0.3
Myocardial infarction	3	0	1.9	0.93
Death	12.5	17	14	0.87

Table 2: Outcomes. This table compares the outcomes between both groups and includes stroke as well as myocardial infarction and death after 5 years of follow up.

Characteristics	P-value before matching	P-value after matching
Age	0.006	0.4
Smoking	<0.001	0.82
DM	<0.0001	0.73
HTN	<0.002	0.45
CAD	<0.0001	0.99
Aortic Stenosis	<0.0001	0.97
CKD	<0.002	0.61
ACE Inhibitor	<0.002	0.85
Antiplatelets	<0.001	0.83
EF<60%	<0.009	0.86
Atrial Fibrillation	<0.007	0.3
Gender	0.09	
Beta Blocker	<0.02	0.7
Calcium Blocker	0.07	0.2
Statin	0.08	0.4

ACE: Angiotensin Converting Enzyme Inhibitor, CAD: Coronary Artery Disease, CKD: Chronic Kidney Disease, EF: Ejection Fraction, HTN: Hypertension

Table 3: Characteristics and demographics Covariates before and after adjusting for propensity score. Adjusting for PS, covariates are found to be balanced between the groups.

events occurred after endarterectomy. The development of myocardial infarction, either spontaneous or perioperative, after the date of recruitment in the study was not different between the screened and the control groups, (3% vs 0%, p=0.93 respectively).

Discussion

Historically, adults with asymptomatic carotid stenosis have been considered at increased annual risk of 2.5% for ipsilateral carotid territory ischemic stroke according to studies before the modern medical therapy [4,5]. Its prevalence ranges from 7% in women to 12% in men older than 70 years old. The latest USPTSF guidelines which advise against noninvasive imaging for carotid stenosis in all asymptomatic patients [2]. Despite these advisories the asymptomatic Medicare beneficiaries are increasingly being evaluated with noninvasive imaging studies for this indication [6]. Looking back at the surgical Data especially Cardiopulmonary Bypass population Schwartz et al. initially showed that 62.5% of postoperative strokes were believed to be related to ipsilateral carotid disease [7]. In another study by Stamou et al., only 25 experienced stroke with only in 0.1% of the deficit being attributable to carotid ipsilateral disease [8].

Our study was the first to match high risk patients who were screened for asymptomatic carotid artery stenosis and to follow them retrospectively for at least 5 years. 30% of the patients were followed up at 9 years status post ultrasound screening. The rate of ipsilateral stroke was much less than what was previously reported. This could be attributed to adherence with antiplatelet, statin and antihypertensive therapy. The lack of benefit in screening was demonstrated by the lack of difference between the incident of strokes over the follow up years in both groups. Though these results might not be totally generalized due to the small sample size and the non-randomized nature of the study, its results are in accordance with previous large trials and the latest USPTSF guidelines which advise against noninvasive imaging for carotid stenosis in all asymptomatic patients.

Our subgroup analysis has shown that even in the participants who had CABG performed, those who had an imaging evaluation of the carotid arteries did not experience less strokes preoperatively (Figure 3). Pre-operative carotid screening Coronary bypass graft surgery is controversial [9]. Several predictors have been found to correlate with a higher risk of perioperative stroke from ipsilateral carotid disease. Guidelines have concluded that the higher the score according to

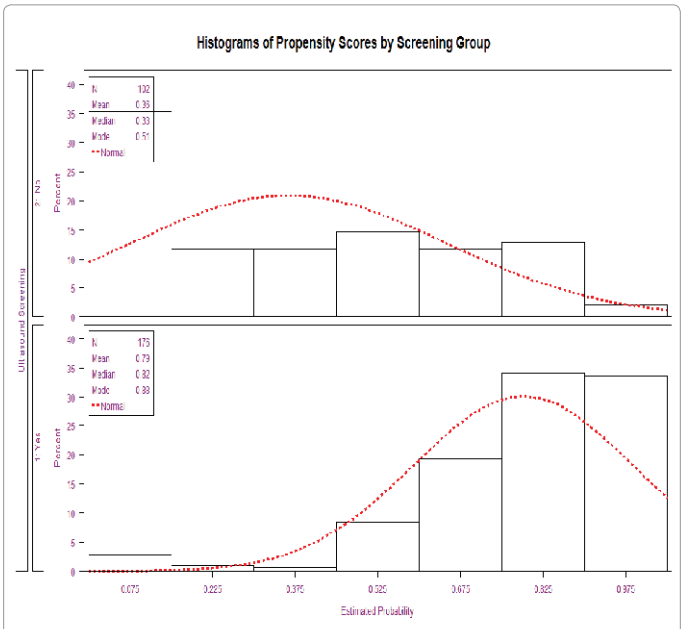
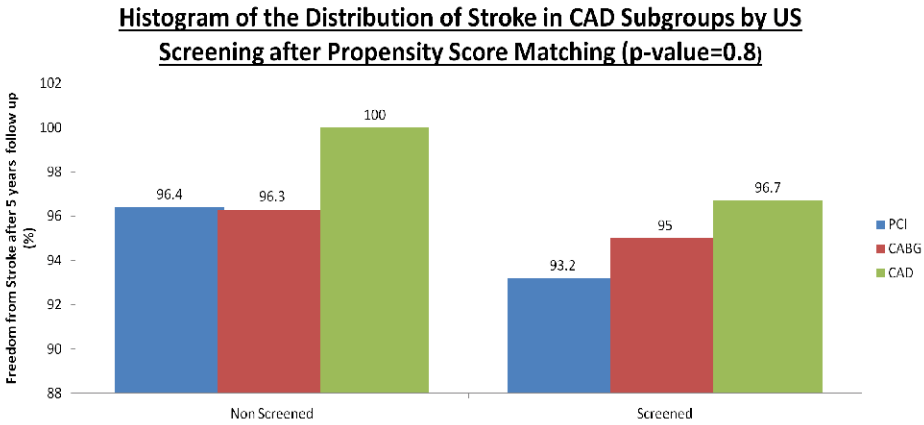


Figure 2: Histogram of propensity scores by screening group.



CABG: Coronary Artery Bypass Graft, CAD: Coronary Artery Disease, PCI: Percutaneous Coronary Intervention, US: Ultrasound

Figure 3: Histogram of the distribution of stroke in CAD subgroups by US screening after propensity score matching (p-value=0.8).

those variables the more plausible is the indication for preoperative screening. Previous cerebrovascular events and left main coronary disease were strongly associated with stroke occurrence. As part of this study design such patients were excluded and the study was not powered to evaluate left main disease as a standalone variable. Thus our results cannot be generalized to the population of patients with high preoperative score for stroke occurrence who still might benefit from preoperative screening according to previous studies [10].

Our data is also consistent with other studies that have demonstrated that the risk of stroke in asymptomatic and clinically significant carotid stenosis was very low while on contemporary medical treatment. A recent study by Marquardt et al. which included 301 patient- years had shown that only six ischemic events occurred after a three years follow up [11]. In addition no benefit seems to be derived from adding an interventional therapy to medical treatment in asymptomatic patients [12].

Limitations

This is a single center retrospective cohort study. The limitations of such a design are known. The application of a propensity score compensates for the non randomization does not take account for the referral bias that occurs in such a cohort. This study did not consider left main coronary artery disease or peripheral artery disease as risk factors either. All these limitations make the results of the study non generalizable to any high risk patient with coronary artery disease and diabetes.

Conclusion

In the Asymptomatic Carotid Atherosclerosis Study (ACAS) trial, screening was not found to be beneficial in reducing stroke and death but the subgroups of patients such as those with diabetes and coronary artery disease was not studied. This retrospective study is the first to show that even in this high risk group of diabetics with established coronary artery disease the incidence of stroke was not lower in the screened group while on contemporary medical treatment. It is also more representative of the real world patients than randomized trials. This study is limited by the small number of patients included as well as by referral bias that was partially removed by propensity score analysis.

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