Screening for asymptomatic carotid stenosis should not be performed. Uses and abuses of diagnostic tests in asymptomatic people

Experts refuse to learn from history until they make it themselves and the price for their arrogance is paid by the innocent. Preventive medicine is too important to be led by them.

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BACKGROUND

Recent U.S. Preventive Services Task Force (USPSTF) recommendation statement about screening for carotid artery stenosis in asymptomatic adult population is impressive. This procedure is well recognized as the prelude to carotid surgery or angioplasty to prevent stroke in patients with significant lesions. (1)

The U.S. Preventive Services Task Force (USPSTF) recommends against screening for asymptomatic carotid artery stenosis (CAS) in the general adult population (grade “D” recommendation). In 1996, the USPSTF concluded that evidence was insufficient to recommend for or against screening of asymptomatic patients for carotid artery stenosis by using physical examination or carotid ultrasonography; however, in this last update this is a grade D recommendation, which means that the USPSTF recommends against the preventive service. There is moderate or high certainty that the service has no net benefits or that the harms outweigh the benefits, and, in consequence, discourages the use of this service. This short and conclusive phrase appears to go against the intuitive perception of many physicians, who, according to the results of clinical trials, think that revascularization, and especially carotid endarterectomy, reduces the risk of events.

In addition, to accept the usefulness of screening for asymptomatic carotid stenosis we should assess not only the effectiveness of the procedure but also other important issues such as the validity of the screening test (carotid artery ultrasound) evaluated by sensitivity, specificity, positive and negative predictive values, which are related with the prevalence of the disease investigated.

In this way we shall analyze the logical relationships among these variables, which might also be considered before an institution as the USPSTF recommends for or against a method for population screening.

We shall start discussing the evidence available on revascularization of the carotid artery in asymptomatic people, perhaps the condition more familiar to clinicians, and then we shall break down the rest of the concepts less recognized. In this way, we may understand the reasons of this devastating recommendation against population screening.

ESTIMATE OF THE MAGNITUDE OF NET BENEFIT OF CAROTID ARTERY REVASCULARIZATION IN ASYMPTOMATIC PATIENTS

Two of five published randomized clinical trials were excluded from the analysis. The WRAMC (Walter Reed Army Medical Center) study was excluded because it did not use ultrasonographic assessment of carotid artery stenosis, had few participants, and used unclear definitions of outcomes. The MACE (Mayo Asymptomatic Carotid Endarterectomy) study was not included because of its small number of participants and lack of aspirin treatment in the surgical group.

The VACS (Veterans Affairs Cooperative Study) is a fair-quality trial performed in 1993, that included 444 men with 50% to 99% stenosis confirmed by angiography who were followed for a mean of 4 years. All participants were male, and the mean age was 64.5 years. The participants had a generally high cardiovascular risk: 63% had hypertension, 50% were current cigarette smokers, and 30% had diabetes. After 5 years, no significant differences were reported in the incidence of perioperative mortality and stroke: 44.2% and 41.2% in the medical treatment group and surgical group, respectively, RR 0.92 (95% CI 0.69-1.22).

The next two good-quality studies were the ACAS (Asymptomatic Carotid Atherosclerosis Study), published in 1995, and the ACST (Asymptomatic Carotid Surgery Trial), in 2004. (2)

The ACAS included 1,659 patients -less than 4% of the patients assessed- with angiographically confirmed carotid artery stenosis 60% or greater. The mean age of participants was 67 years, mean follow-up was 2.7 years and the participants had high cardiovascular risk: 64% had hypertension, 26% smoked cigarettes, and 23% had diabetes; about 20% had had contralateral transient ischemic attack or stroke. Af-
ter 5 years, the incidence of stroke or perioperative death and subsequent homolateral stroke was 11% and 5.1% in the medical treatment group and surgical group, respectively, RR 0.47 (95% CI 0.28-0.78), with an absolute risk reduction of 5.9% that was not significant in the subgroup of women.

The international, multicenter ACST randomly assigned 3,120 persons with carotid artery stenosis 60% or greater and followed them for a mean of 3.4 years. The mean age was 68 years, and the participants also had high cardiovascular risk: 65% had hypertension, 20% had diabetes, and 24% had contralateral carotid endarterectomy. Medical treatment was similar to what is currently prescribed; aspirin was widely used and more than 50% of the patients were receiving antihypertensive medications and statins. The degree of coronary artery stenosis was determined by ultrasonography. Angiography was not required, but it was often used for confirmation during the first few years of the study and less frequently used in the final years. The 5-year rate of perioperative death or any stroke was 11.8% versus 6.4% in the medical treatment group and surgical group, respectively (absolute risk reduction 5.4% [95% CI, 2.96 to 7.75%]). About half of the strokes prevented by carotid surgery were incapacitating.

Benefits
The 2 largest and highest-quality trials have shown an absolute reduction of stroke and perioperative death at 5 years of approximately 5% from carotid endarterectomy compared with medical treatment for stenosis 60% to 99% in selected patients with selected surgeons.

Limitations
The participants and surgeons in the randomized clinical trials were highly selected, which reduces the possibility of extrapolating these findings to the primary care setting. In addition, the 30-day perioperative results did not include a possible complication as acute nonfatal myocardial infarction. Another important limitation is that the medical management group in the trials was poorly defined, was not kept constant over the course of the study, and was probably not comparable to current standards of optimal medical management.

We must remark that none of the studies demonstrated a reduction in mortality.

WHAT IS THE ACCURACY AND RELIABILITY OF ULTRASONOGRAPHY TO DETECT CAROTID ARTERY STENOSIS 60% TO 99%?
There are two meta-analyses on the accuracy of ultrasonography to detect clinically important stenosis.

The meta-analysis by Nederkoorn and colleagues from 2003 estimated the accuracy of carotid duplex ultrasonography using digital subtraction angiography as the reference standard; this meta-analysis was rated as fair quality because it had limited sources for studies and did not have information on the standard appraisal of studies. Carotid duplex ultrasonography had a sensitivity of 86% (95% CI, 84% to 89%) and a specificity of 87% (CI, 84% to 90%) for detecting carotid artery stenosis 70% to 99%.

A second meta-analysis published in 2005, was rated good quality because of the comprehensiveness of sources and search strategies, the explicit selection criteria, and the standard appraisal of studies. This meta-analysis found a sensitivity of 90% and a specificity of 94% for carotid duplex ultrasonography to detect carotid artery stenosis 60% or greater.

For a better understanding of the concepts of sensitivity and specificity, we might think that an ideal perfect test exists. This means that the test might detect all sick people; in other words, all the sick would have a “positive test”. The “sensitivity” of a test is its ability -in percentage- to detect sick people. Obviously, the sensitivity of a perfect test should be 100%.

But, at the same time, a test is useful to rule out the disease; in the case of a perfect test, we should be able to identify 100% of those who are not ill. This is the specificity of a test.

However, as medical diagnostic tests are always “less than perfect”, no tests have a 100% sensitivity; therefore the sick population is composed of those people with a positive test (true positives, TPs) and those with a negative test (false negatives, FNs) People with a negative test who are not actually ill (true negatives, TN) coexist with those who have a positive test but are not ill (false positives, FPs); this happens as sensitivity is less than 100%.

According to the values reported in the last meta-analysis, in patients with carotid artery stenosis greater than 60%, carotid ultrasound may detect 94 patients (TPs) but will fail to identify 6 patients (FNs) out of 100 with significant carotid lesions. In turn, of 100 patients with stenosis lower than 60%, ultrasound will detect 92 (TNs) and will consider ill 8 patients (FPs).

PREVALENCE OF CLINICALLY IMPORTANT CAROTID ARTERY STENOSIS

Importance of Ultrasound Predictive Values
The prevalence of clinically important carotid artery stenosis (60% to 99%) diagnosed by ultrasound is about 1% or less in general primary care population, and 1% in people aged 65 or greater according to population studies.

Figure 1 shows the number of true and false results, whether positive or negative, in a general population of 100,000 asymptomatic adult patients.

It can be noted that although sensitivity and specificity are high, the prevalence is low, 1% (1 patient with significant stenosis detected by ultrasound and 99 patients without clinically significant lesions);
FPs are 8.4-fold greater than TPs and predictive value is slightly greater than 10%. This means that out of 100 asymptomatic adult patients with “labeled” carotid artery stenosis of 60% or greater, only 10 patients will have this condition (confirmed by cerebral angiography) and 90 patients will not have carotid artery stenosis clinically significant.

In turn, the negative predictive value would be very high, 99.9%.

If we referred patients to surgery based only on this diagnostic technique, obviously a great group of patients would be subjected to an unnecessary risk. Let us see those risks.

### WHICH ARE THE HARMS OF A CAROTID ENARTERECTOMY?

There are 14 observational studies that evaluated carotid endarterectomy complications in patients with asymptomatic carotid artery stenosis. The mean age of patients ranged from 67 to 74 years, most participants were white and almost all participants in the 2 Veterans Affairs studies were male, whereas the other studies included one third to 50% of women.

The 30-day perioperative stroke or death rates in asymptomatic persons in the Medicare and New York City database studies ranged from 2.3% to 3.7%. One Veterans Affairs study showed a perioperative stroke or death rate of 1.6%. A systematic review found an overall stroke and death rate at 30 days of 3.0% in studies published since 1995. (3)

Some observational studies reported an incidence of perioperative nonfatal myocardial infarction of approximately 0.7% to 1.1%. Patients with more comorbidities had a nonfatal myocardial infarction rate of up to 3.3%. The rate of nonfatal perioperative myocardial infarction reported for the surgical group in the clinical trials varied from 1.9% in VACS to 0.6% in ACST with no systematic search of patients.

There is little information available on specific rates of other complications; however, the VACS reported a surgical complications rate of 3.8% for cranial nerve injuries (none of these injuries were permanent), 25% for hypertension and 5.2% for hypotension. (4)

There are no studies on anxiety or labeling among people with false-positive results on ultrasonography screening.

### BALANCE BETWEEN BENEFITS AND RISK OF STROKE IN CAROTID ENARTERECTOMY

Patients Referred to Surgery Only with Carotid Ultrasound

If all patients with a positive carotid ultrasound result are referred to surgery, we might consider if the whole population benefits or harms, taking into account that the possibility of a perioperative stroke is 3.1% (as in ACST).

Screening of 100,000 persons will result in 7,920 FPs (see Figure 1) with an incidence of perioperative stroke of 3.1%; thus, 246 strokes will occur.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>TEST Positive</th>
<th>Negative</th>
</tr>
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<tbody>
<tr>
<td>Positive</td>
<td>940</td>
<td>7.920</td>
</tr>
<tr>
<td>Negative</td>
<td>60</td>
<td>91,080</td>
</tr>
<tr>
<td>Total</td>
<td>1,000</td>
<td>99,000</td>
</tr>
</tbody>
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TP (sensitivity) = 1.000 x 0.94 = 940
FN (1 - sensitivity) = 1.000 x 0.06 = 60
TN (specificity) = 99,000 x 0.92 = 91,080
FP (1 - specificity) = 99,000 x 0.08 = 7,920

**+** Predictive value = \[
\frac{TP}{TP + FP} \times 100 = 10.6%
\]

**-** Predictive value = \[
\frac{TN}{TN + FN} \times 100 = 99.9%
\]

If according to ACST the 5-year rate of perioperative death or any stroke has a reduction of 5.4%, 51 events would be prevented (see the estimation below).

<table>
<thead>
<tr>
<th>ACST 5-year rate of events (stroke + perioperative death)</th>
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<tbody>
<tr>
<td>Medical treatment</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Strokes prevented with surgery = 111 – 60 = 51</td>
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Therefore, if 51 strokes would be prevented but 246 would occur, the final result is 195 more events attributed to the procedure at 5 years.
Patients Referred to Surgery after Carotid Angiography

If we consider digital angiography as the gold standard, we might say it is a perfect test with 100% sensitivity and specificity, without false negatives and, most important, without false positives. Therefore, no patient would be referred to surgery without a carotid stenosis clinically significant.

We should now focus on the risk of stroke after angiography.

In clinical trials performed in asymptomatic patients subjected to carotid endarterectomy, the incidence of non fatal stroke is 1.2% and according to other series persistent neurological complications may be about 0.5%.

If all the 8,860 patients with a positive ultrasound (TP 940 + FP 7920) underwent angiography, this procedure would confirm 940 TPs and rule out 7,920 FPs. But as angiography induces non fatal stroke in 1.2% of cases, this means that 106 strokes would occur out of the 8,860 studies. And 51 events would be prevented with surgery. So, ultrasound plus angiography would produce 55 more events. Although this number is lesser than the one obtained referring patients to surgery with carotid ultrasound only, it still produces harm.

We know that about 1% of the adult population has a significant carotid artery stenosis, and that the prevalence of this condition is greater among smokers, patients with hypertension or with heart disease, but unfortunately there are no clinically useful stratification risk tools.

As we have seen, when the prevalence of carotid artery stenosis is so low in the population, carotid ultrasound results in a great number of false positives, despite its sensitivity and specificity of approximately 94% and 92%. This is particularly important in terms of screening, as surgery may produce death or perioperative stroke in more than 3% of patients. If we perform an angiography to all the patients with a positive test in order to minimize the great number of false positives, we have also seen that the incidence of non fatal stroke with this method is 1%.

Treatment of coronary artery stenosis in selected patients by selected surgeons, with an incidence of postoperative death or stroke less than 3%, might lead to approximately a 5% point absolute reduction in strokes over 5 to 6 years compared to controls. Can this difference be sustained if the procedure is generalized without selecting patients and surgeons? This is a pending issue.

Another important limitation is that the medical treatment of patients in clinical trials was not well defined and it did not include intensive treatment of blood pressure and lipid control as nowadays. An intensive medical treatment would have probably reduced the differences among groups.

We should not forget that surgical benefit is seen later, after the initial impact of morbidity and mortality related to endarterectomy; curves cross from net harm to net benefit at about 1.5 years after carotid endarterectomy for men, and at nearly 3 years after carotid endarterectomy for women and we still do not know the outcomes at 10 years.

When a patient comes to consultation for a specific condition, such as fleeting blindness, the risk derived from complementary studies is acceptable. On the contrary, screening deals with apparently healthy subjects in whom harm, stigmatization and costs related to screening are especially important and generally ignored in our attempt to reach an earlier diagnosis. The medical and ethical standards of screening should be higher than with diagnostic tests. Any adverse outcome derived from a screening test is iatrogenic and completely preventable.

It is preferable to have a direct evidence of the accuracy of a test from randomized clinical trials before adopting it as a screening method. In accordance with data available in medical literature, the USPSTF indirectly concludes that screening for carotid artery stenosis produces more strokes than those prevented with carotid endarterectomy. However, the study has not found any “direct” evidence that screening of asymptomatic patients for carotid artery ste-
nosis with ultrasound reduces (or an eventual increases) fatal and non fatal stroke.

There is a direct evidence of the effect of screening for other diseases, such as aortic abdominal aneurysm (AAA); several studies have been designed to assess its benefits. In this situation, screening with abdominal ultrasound is then confirmed with a computed tomography that does not produce any harm.

The Multicentre Aneurysm Screening Study (MASS) (6-7) randomized 67,770 men aged 65-74; 33,887 were assigned to the control group and 33,883 were invited to screening with abdominal ultrasound. Mean follow-up was 7.1 years; mortality rates were 0.48/1000 persons-year (105/33,883) and 0.91/1000 persons-year (196/33,887) in the screening group and control group, respectively; RRR 47% (95% CI 32% to 58%). The incidence of non fatal ruptured aneurysm in the invited group was half of that of the control group (30 to 61, respectively). All-cause mortality showed a reduction of 4% that was statistically significant (95% CI 95%, 0% to 7%).

A Cochrane meta-analysis of 4 randomized and controlled trials (RCTs) of screening for aortic abdominal aneurysm (Cochrane Database of Systematic Reviews, 01/26/2007) pooled more than 127,891 men and 9,342 women, between 65 and 83 years, and found a mortality risk reduction of 40% in men (95% CI, 22% to 53%).

CONCLUSIONS

Screening of apparently asymptomatic people may result in benefit (screening for aortic abdominal aneurysm) or harm (screening for carotid artery stenosis). The difference between a diagnostic test and a screening test is that the latter is performed in apparently healthy people. Therefore, although carotid ultrasound has a high sensitivity and specificity, its positive predictive value is poor when it is applied to populations with a low prevalence of a disease, in this case to adult population with significant carotid artery stenosis (1%).

When a stratification tool may produce the same harm which pretends to prevent, the decision to adopt it as a screening test should be carefully weighted, as any adverse outcome produced by a screening test is iatrogenic and totally preventable.

But we should not feel discouraged, as we still have the possibility to focus on primary prevention which reduces the incidence of stroke 60% to 80% if we optimize medical treatment with antihypertensive drugs, aspirin and statins and encourage smokers to quit the habit, especially in high-risk populations.

BIBLIOGRAPHY