Accuracy of Auscultation for Carotid Bruit in Asymptomatic Patients to Screen for Carotid Artery Stenosis and Stroke Outcomes: a Systematic Review

By

Daniel J. Watford

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Structured Abstract

Background: Stroke is currently the 4th leading cause of death in the United States. After a systematic review in 1996, the USPSTF concluded that the evidence was insufficient to recommend for or against screening of asymptomatic people for carotid artery stenosis (CAS) using auscultation for carotid bruit during physical exam. Using the reference standard of 70-99% stenosis on carotid angiogram, they determined the sensitivity and specificity of a carotid bruit to be 63-76% and 61-76% respectively for identifying CAS of this degree.

Purpose: To examine the evidence since the 1996 USPSTF review on accuracy of auscultation for carotid bruit as a screening test for CAS and subsequent stroke outcomes to provide accuracy data and help afford better guidance on the utility of this means of screening for CAS in asymptomatic patients in the general population.

Data Sources: MEDLINE search (January 1996-present), recent randomized controlled trials (RCTs), cohort studies, and diagnostic accuracy studies, reference lists of retrieved articles.

Study Selection: English language studies were selected to answer the questions: (KQ1) What is the accuracy of auscultation for carotid bruit to predict fatal or nonfatal ischemic stroke or TIA? (KQ2) What is the accuracy of auscultation for carotid bruit to detect potentially clinically important CAS (60% to 99%)? Study types were RCTs or cohort studies of asymptomatic patients at least 19 years of age, from which data on cerebrovascular outcomes could be extracted. Also they could be diagnostic accuracy studies comparing auscultation for carotid bruit to the gold standard of angiography in asymptomatic patients at least 19 years of age.

Data Synthesis: There were no RCTs of screening for CAS by auscultation for carotid bruit. Two included cohort studies showed the sensitivity and specificity of carotid bruit to identify subsequent stroke in asymptomatic patients to be 9.1-13.4% and 93.75-96.7% respectively with

false-negative rates of 86.6-90.9%. No studies met inclusion for KQ2 due to improper gold standard, but 2 cohort studies and a systematic review using the reference of duplex ultrasound, the sensitivity and specificity for identifying CAS ≥ 60% were 56.25-57.5% and 80-98%.

Limitations: There were no RCTs of screening for CAS to answer KQ1 and the included cohort studies were conducted in selected populations with diabetes or isolated systolic hypertension. These only focused on stroke without assessing the outcome of TIA. No accuracy studies met inclusion for KQ2 that used the gold standard of angiography. The quality of included studies was only fair on average.

Conclusions: The sensitivity and specificity of auscultation for carotid bruit are low and exhibit poor accuracy for a screening test. Such low values would result in high false-positive and false-negative rates, both for identifying CAS as well as subsequent stroke in the asymptomatic population. Inadequate certainty of the benefit of screening for CAS in the general asymptomatic population, lack of a reliable means to delineate a more distinct group to screen in, and the poor accuracy of auscultation for carotid bruit in the primary care setting makes it difficult to consider widespread use of this screening test in the general population. Until we know with reasonable certainty that such screening leads to reduced strokes and better understand how to delineate the best group of people to screen in, I do not recommend the use of auscultation for carotid bruit in the primary care setting as a screening test for CAS and future cerebrovascular outcomes in asymptomatic patients.

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Accuracy of Auscultation for Carotid Bruit in Asymptomatic Patients to Screen for Carotid Artery Stenosis and Stroke Outcomes: a Systematic Review

Introduction:

Stroke is currently the 4th leading cause of death in the United States (1). Approximately 6.8 million Americans over 20 years of age have experienced a stroke at some point in the past. The prevalence of past stroke is estimated to be about 2.8% (2). This prevalence estimate is derived by taking prevalence results of the health interview portion of the National Health and Nutrition Examination Survey (NHANES) from 2007-2010 and applying these figures to national Census population estimates for 2010. Thus, this relies heavily on national survey data. Each year approximately 785,000 Americans experience a stroke, with 610,000 of these people experiencing a first stroke. This translates into an average of one person suffering a stroke in the United States every 40 seconds (2). These are extrapolations to the current US population from data of various studies including the Framingham Heart study and the Cardiovascular Health Study.

The consequences of stroke are often quite devastating. A recent study showed stroke to have a mortality rate of 4.5% due to the acute event or within the initial 30 day period following the event; 20 year mortality rate is as high as 27% for ischemic stroke in adults of age 18 to 50 years (3). Stroke accounted for nearly 1 out of every 19 deaths in the US based on data from 2009 (4). Beyond just mortality, stroke is also the leading cause of severe long-term disability in the United States, frequently resulting in hemiparesis, severe cognitive defects, and significant dependence in activities of daily living among other consequences (5, 6). Therefore, it is clear that the burden of stroke in our country is quite substantial.

However, there has been improvement as the current stroke mortality rate represents an almost 70 percent reduction since 1950 and a decline of nearly 37% since 1999 (2, 4). A great

deal of this has been attributed to better control of important risk factors such as hypertension and tobacco use in the population.

More recently, specifically since the publication of the Asymptomatic Carotid Surgery Trial (ACST) in 2004, there has been increased use of carotid endarterectomy (CEA) as well as carotid angioplasty and stenting (CAAS) as revascularization techniques to treat patients whose strokes may be attributable to carotid artery stenosis (CAS). Major randomized controlled trials (RCTs) have shown that CEA effectively reduces stroke in symptomatic people with severe carotid artery stenosis (7, 8). In this case symptomatic is defined as those who have previously suffered a transient ischemic attack (TIA) or stroke. Thus there is benefit to evaluating and treating these symptomatic patients. However, even with the results of the ACST, there is still much less clarity when it comes to asymptomatic patients who have had no previous cerebrovascular events or significant neurologic symptoms referable to the carotid artery. Though carotid artery stenosis can be identified in asymptomatic patients as well, it is not clear whether screening them for CAS and treating with revascularization such as CEA or CAAS leads to reduction in stroke (9).

After completing a systematic review on the topic of screening asymptomatic people for CAS in 1996, the USPSTF concluded that the evidence was insufficient to recommend for or against screening of asymptomatic people for CAS using auscultation for carotid bruit during physical exam or by carotid ultrasound (10). This was based partly on new evidence at the time from the Asymptomatic Carotid Artery Study (ACAS), a large RCT involving 1662 asymptomatic patients with carotid stenosis of 60 percent or greater. Though this trial showed some benefit in the surgical group with relation to stroke incidence and death compared to the control group over the course of 2.7 years of follow-up, these results depended significantly on

the rate of perioperative complications involved. The interventions in this trial were performed in centers by surgeons with very low complication rates. There was also very little information available at the time on what the complication rates for CEA were in the general population. Thus the generalizability of the results from the ACAS trial to the general public was unclear, making it difficult to determine if screening asymptomatic patients for CAS and then treating them yields benefit in this population. These reasons were the major contributors to the USPSTF's 1996 conclusion that there was insufficient evidence to recommend for or against screening (10).

Specifically concerning auscultation for carotid bruit, the USPSTF found this to be an imperfect screening test for CAS with ample inter-observer variation among clinicians performing the test. Using stenosis of 70-99% on angiogram as the reference, they also found this test to have poor sensitivity and specificity; 63-76% and 61-76% respectively (10).

Since the 1996 review more data has emerged and further studies have been conducted attempting to investigate the role of screening and treatment for CAS in asymptomatic patients as well as complication rates from treatment in community and academic settings. This includes the ACST, one of the largest multicenter RCTs on the topic published in 2004 that involved 3120 asymptomatic patients with CAS of 60 percent or greater (7). Due to this new evidence the USPSTF conducted an update in 2007 to their previous review on screening for CAS. However, due to their findings in 1996 and a paucity of new evidence on the topic, the USPSTF decided not to focus on auscultation for carotid bruit during physical exam as a screening tool for this 2007 update (9). After reviewing the new evidence in 2007, the task force concluded that screening would result in considerable false-positives leading to harms from confirmatory testing or unnecessary surgeries, namely carotid endarterectomy. These harms outweighed the potential

benefit of preventing stroke from these procedures, leading to the USPSTF's updated recommendation not to screen for asymptomatic CAS in the adult population (9).

Relevance of Screening for CAS and its Related Outcomes

Effective screening tools are designed to identify individuals in a population that may be at increased risk for a disease or disorder that would otherwise go unrecognized until a later time. If identified early through screening, these individuals may or may not be able to receive early treatment or intervention that could reduce morbidity and/or mortality from the disease or disorder in question. The use of screening is especially useful for diseases that have an especially detrimental course if identified at later stages as opposed to catching it earlier. Based on guidelines drafted by the World Health Organization (WHO), screening should only be applied if the disorder in question is an important health problem and there is a treatment for the disorder (11). Also the magnitude of benefits from screening should be weighed against the magnitude of harms to determine the net benefit that would arise from a specific screening protocol (12). Clearly stroke is an important health problem with seriously detrimental consequences if not prevented. Therefore, it would be advantageous to identify those people at risk for stroke prior to the actual event so that they can be treated early and possibly avoid such a detrimental event. As CAS is a risk factor for stroke and accounts for approximately 10-15% of strokes in the general population based on crude extrapolation from stroke prevalence numbers by type and epidemiological data, screening for this is important to potentially avoid the serious consequences of stroke (9). Screening tests require confirmation using further testing that is more certain but may also be more time-consuming, invasive, expensive, and may cause harms. Thus, initial screening tests are often simpler, less invasive, and require less time to administer and evaluate. Therefore, screening for CAS by auscultation for carotid bruit during physical exam

may be suitable as a screening test because it is very inexpensive and is a simple, non-invasive test that is quick to administer.

This review is an adjunct to a review by the USPSTF to update their previous 2007 review of screening for CAS. The review will revisit auscultation for carotid bruit as a screening test for CAS as in the 1996 review, with angiography as the confirmatory testing. It draws upon the 1996 and 2007 recommendations and looks at the evidence on accuracy of carotid bruit auscultation in CAS screening. I will investigate the focused question of what is the accuracy of auscultation for carotid bruit to predict fatal or nonfatal ischemic stroke or TIA ipsilateral to CAS. As another key question, I will also investigate the accuracy of this screening method to detect potentially clinically important CAS (60-99%). I am focusing on accuracy or the ability of auscultation to identify actual stroke outcomes as well as CAS of 60-99% as opposed to reliability or the ability of auscultation measurements to be reproducible under the same conditions from one measurement to the next.

It is important to note that 60-99% stenosis is the range that is generally considered in several major studies and most guidelines to represent clinical significance for ischemic outcomes and also the point at which revascularization procedures such as CEA are indicated. However, the evidence does not clearly show that the 60% lower bound actually designates the point at which risk of ischemic outcome in individuals increases greatly above that of others in the general population with stenosis values slightly below or above this cutoff point. In fact the most significant increase in risk has actually been noted at ranges above 70%, which is also the cutoff where the most benefit is seen from endarterectomy based on symptomatic patients in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) as well as in asymptomatic patients in the ACST (13, 14). Nonetheless, this review will focus on the range of

60-99% to represent clinically important CAS based on its frequent use in the scientific literature. This review will systematically take into account the newly available evidence since the previous USPSTF reviews with the hope of providing healthcare providers with updated guidance on the utility of auscultation for carotid bruit as an effective screening test for predicting cerebrovascular events from CAS.

Background:

What is Carotid Artery Stenosis?

Carotid artery stenosis is defined as the pathologic narrowing of the lumen of the extracranial carotid arteries due to atherosclerotic disease. The relationship between the degree of narrowing and the risk of stroke has not been clearly demonstrated and this relationship is further complicated largely because many patient factors others than the degree of narrowing affect the risk of stroke. A clinically significant degree of carotid stenosis may be very different in an elderly male patient with a smoking history and diabetes than it would be in a younger female patient with hypertension but no smoking history. Because of this uncertainty in how degree of carotid narrowing relates to stroke risk, there is variation in the definition of clinically significant CAS. Major RCTs including the ACAS and the ACST defined CAS as 60-99 percent while some earlier trials including the NASCET looking at symptomatic patients used 50-99 percent. As mentioned, these studies found that the highest risk of stroke and the greatest benefit from treatment manifested at CAS levels of greater than 70%, though there was some modest benefit in those with CAS of 50-69% with a 5-year absolute risk reduction of 6.5% for ipsilateral stroke after treatment with CEA (13, 14).

Prevalence and Clinical Importance of CAS in the General Population

A recent systematic review and meta-analysis published in 2009 that included 40 cross-sectional and cohort studies dating back to 1983 found variation in prevalence figures of CAS

based on differences in certain demographic factors, CAS cut-off points used for identification, and the methods used to grade stenosis (15). This study had several limitations though, mostly due to a pretty large degree of heterogeneity among included studies. This especially applied to differences in the way patients were recruited for the various studies, which affects their representativeness of the general population. As mentioned, there was also variance in the method of measuring the degree of stenosis between the studies such as NASCET versus ECST methods as well as differences in response rates of participants in the different studies, with older patients responding less. This lends to potential selection bias and likely underestimation of overall prevalence rates as asymptomatic CAS is believed to be more prevalent in older individuals. Some of the included studies were also a bit outdated as seven of them were published prior to 1990. More recent prevalence estimates may differ due to changes in current management of CAS risk factors and use of various medications such as statins in those at risk for CAS and other vascular outcomes. The review included studies from US populations as well as from various European countries, Mexico, Japan, China, and Australia. The ages of patients varied amongst the studies, ranging from 18 to 101 years old. There was also variance in the sex distributions between the included studies. As a result there was significant variation in prevalence estimates across the included studies, which affects our ability to draw concrete conclusions from the study and generalize the findings to specific populations such as that of the US.

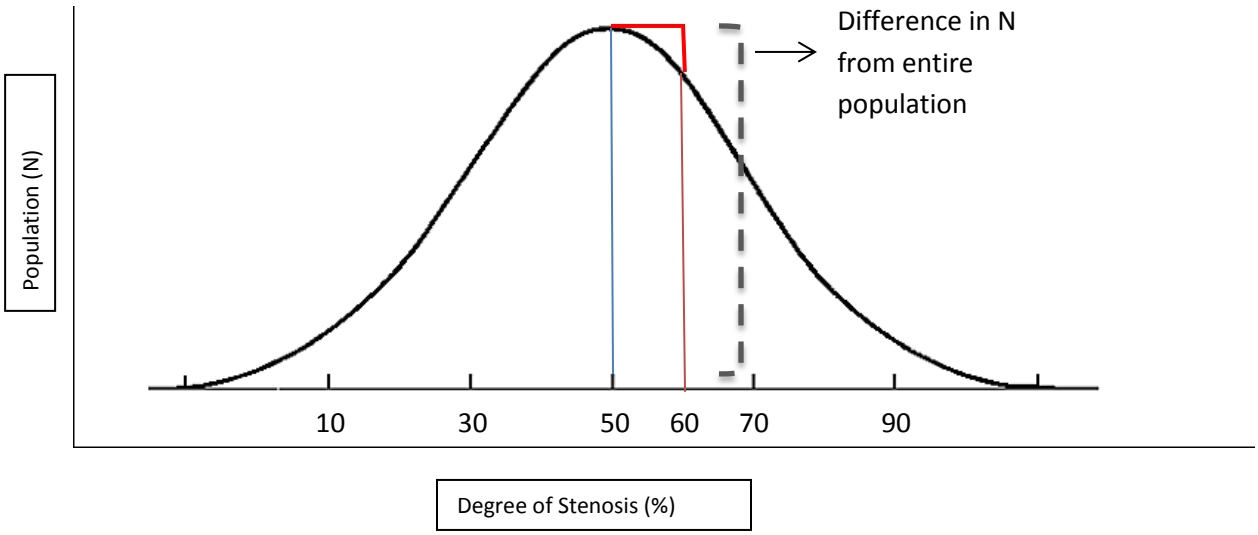
The review findings showed a pooled prevalence of 4.8 percent (men) and 2.2 percent (women) for CAS greater than 50 percent stenosis in people less than age 70. In those older than age 70 these numbers were 12.5 percent and 6.9 percent respectively. They found that the prevalence of CAS increases with age in both men and women, but men of all ages have higher

prevalence estimates than women. The overall pooled prevalence of 70 percent or greater stenosis was 1.7 percent. The prevalence of this same degree of stenosis in asymptomatic people at least 80 years old was quite small at 3.1 percent in men and 0.9 percent in women (15, 16). The analysis for the most recent USPSTF recommendation on the topic estimated the prevalence of people with unknown CAS to be 1 percent or less in the general population and 1 percent in people at least 65 years of age (9). This was mainly based on data from the Framingham and the Cardiovascular Health Studies.

A clinically significant degree of CAS is considered to be the degree of stenosis that corresponds to a high enough increased risk of stroke, leading to a change in clinical management beyond that for those considered to be at baseline risk. This poses quite a challenge to define, especially in asymptomatic people, as the risk of stroke depends on much more than solely the level of carotid lumen narrowing. Several studies including the Cardiovascular Health Study have shown an increased risk of stroke with greater degrees of stenosis as well as multiple risk factors (17, 18). The majority of studies investigating CAS treatment considered clinically significant stenosis to be ≥ 50 or ≥ 60 percent. This difference is not a trivial one though as a relative cutoff point difference of 10% stenosis amongst the general population would encompass a huge amount of people. Essentially by setting such a cutoff point, you are treating what is really a continuous variable as a categorical one. Since degree of carotid stenosis is truly a continuous variable, there is a wide spectrum across which people in the population will fall. One way to picture this is on a bell curve with number of people on the y-axis and degree of stenosis on the x-axis. People with the very high and very low degrees of stenosis would be at the respective extremes with all others falling between these extremes. The bulk of the population would be represented by the more intermediate stenosis values falling in the middle

including those with 50% and 60%, although the actual median probably falls closer to 20-30% depending on the ages being considered. As you follow along the curve, the drop off from a 50% cutoff to a 60% one encompasses a great amount of people when thinking in terms of an entire population. This is shown in figure 1 as the difference in the amount of people classified for 50% versus 60% stenosis is represented by the volume under the curve outlined by the rectangle. Thus, it is important to utilize a cutoff point that is supported by strong evidence of associated risk rather than arbitrarily selecting one based on guidelines and amending under the assumption that what applies to one cutoff point must also apply to a higher one, as in 50% versus 60% stenosis. This phenomenon is commonly known as guideline creeping.

Figure 1: Bell Curve representation of CAS in General Population



CAS-Related Stroke Burden

The percentage of strokes in the general population that are related to CAS is even less clear. The majority of strokes are ischemic, accounting for approximately 87 percent of all strokes (19). Ischemic stroke is the type we are most concerned with in relation to CAS. Few studies have thoroughly investigated the burden of strokes due to CAS although a follow-up study using results from the North American Symptomatic Carotid Endarterectomy Trial

(NASCET) found that as much as 45% of strokes in the territory of asymptomatic carotid arteries with 70-99 percent stenosis were not related to CAS (20). However, this study population was composed of symptomatic patients though they looked at asymptomatic carotid arteries on the contralateral side from previous events. From this data the USPSTF previously attempted to extrapolate the burden from CAS, estimating that CAS is the cause of stroke in less than 15 percent of cases and even less in those that are asymptomatic (9). The population-attributable risk is thought to be 2 to 7 percent (2). The annual risk of stroke in asymptomatic patients with CAS has been decreasing in recent years, in large part due to the improved and higher-intensity medical therapy recommended in these patients (21). In such patients receiving proper medical therapy, recent studies including a systematic review looking at mostly hospital-based data estimated the risk of stroke to be less than 1 percent per year and could be as low as 0.3 percent per year (22, 23). Though this seems like a low percentage, one must still keep in mind the large number of strokes occurring in our country each year. Such a small percentage of a number as great as 785,000 still accounts for a substantial health burden in this population that should not be overlooked.

Risk Factors for CAS

Several important risk factors for clinically significant CAS have been identified. These factors include smoking, hypertension, and heart disease as well as male sex and age greater than 65 years (24-26). Smoking and heart disease are especially linked to greater risk of CAS, yet like the others listed, they actually only lead to small absolute increases in risk. Good studies demonstrate greater than double the relative risk for CAS $\geq$ 50% in patients from each of these risk factors independently. Yet when looking at the absolute risk, the increase is not very large with CAS risks of 4.4% for those who never smoked versus 9.5% for current smokers and 18.2%

for those with heart disease compared to 8% for those without heart disease (24, 26). Results from the Cardiovascular Health Study looking at patients with CAS ≥ 50% found even smaller differences in absolute risk for this degree of stenosis. Their results showed a risk of 7% in current smokers vs. 4% in nonsmokers and the same absolute risks for those with history of coronary artery disease vs. those without respectively (27). In the same study patients with hypertension showed a risk of 5% compared to 3% in those without, 4% for males compared to 5% for females, and 4% for those age 65-75 years compared to 5% for those older than 75 years (27). These small absolute differences in risk do not predict CAS very well and do little to separate patients out in terms of differences in clinical management.

The fact that a risk factor shows incremental statistical increases in risk is not sufficient enough to warrant its use in clinical practice. The use of the risk factor must have real clinical utility so that its identification leads to changes in recommended clinical management. This often requires that such factors raise the risk above an agreed upon threshold that above which management differs from those individuals who's risk falls below the threshold (28). So even with this knowledge of risk factors, we still are unable to clearly separate out the people who possess clinically significant CAS from those without it due to small differences in absolute risk.

Screening for CAS

Screening for carotid artery stenosis is generally performed by auscultation for carotid bruits during physical examination or by noninvasive imaging of the carotid artery, most often by duplex ultrasound. Carotid angiography is considered the gold standard for evaluating the carotid arteries for stenosis but is not recommended as a screening test due to its level of invasiveness, expense, and associated morbidity and mortality. This review focuses on the use of auscultation for carotid bruit as a screening test of clinically significant CAS.

A carotid bruit is defined as an audible sound arising from turbulent blood flow in the carotid artery and often heard through auscultation with the stethoscope. Several older studies have found that carotid bruits in asymptomatic patients have poor predictive value of underlying carotid stenosis and stroke risk. These studies found that the annual incidence of stroke occurring ipsilateral to an asymptomatic carotid bruit is only 1-3 percent (29, 30). In one of these prospective studies looking at 500 patients with asymptomatic carotid bruits in a Canadian population, only 22.6 percent of them were found to have a carotid stenosis of 70-99 percent by Doppler ultrasound (29). Also results from a prospective population study of asymptomatic people $\geq$ 45 years old living in rural Evans County, Georgia showed that out of the patients with a clinically significant carotid stenosis of 70-99 percent, only about half of them have a bruit that can be detected on physical exam (31). A more recent study in elderly patients found that the presence of a carotid bruit translated into a risk for stroke of 1.86 per 100 patient-years compared to 1.21 per 100 patient years in those without bruits. This led to an unadjusted relative risk of 1.53 and 1.29 when adjusted for risk factors over an average follow-up period of 4.2 years (32). This relative risk was not statistically significant after statistical analysis. Some of the poor predictive value of carotid bruit for detecting significant carotid stenosis in asymptomatic people is due to the low prevalence of such levels of stenosis in this population in the first place (33, 34). Previous studies show that carotid bruit may be a better indicator of general atherosclerotic disease than of stroke risk (35, 36).

For these reasons the USPSTF as well as the American Heart Association have previously recommended against the use of this screening for CAS in asymptomatic patients. However, many physicians still continue to employ this as part of their physical examinations in this patient population and often use it to inform their course of care as it is a cheap, non-

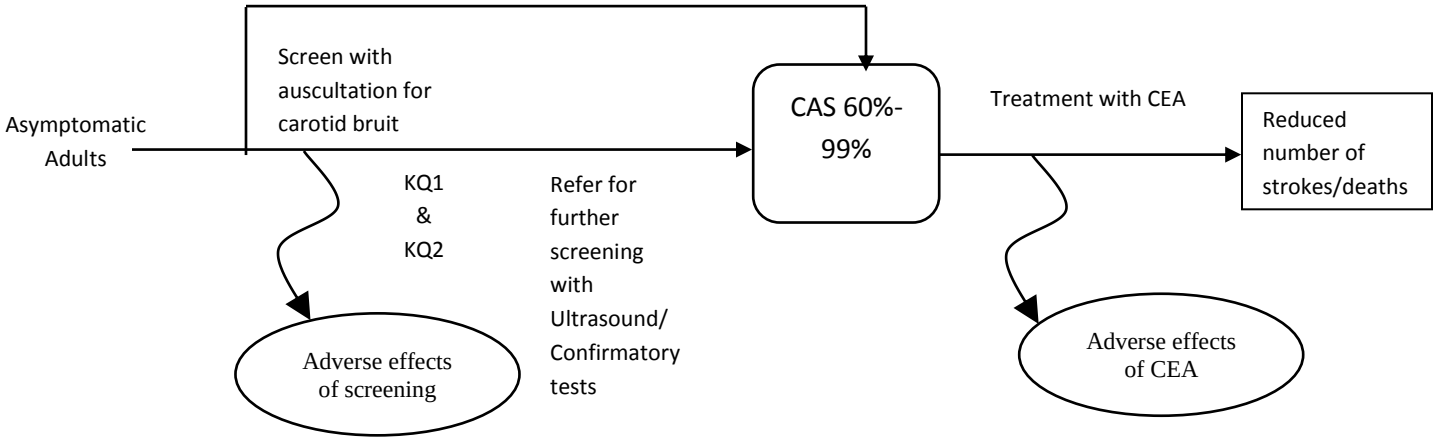
invasive, and relatively easily-administered test. Hopefully this review of the updated evidence on auscultation for carotid bruit will provide accuracy data and help afford better guidance on the utility of this means of screening for CAS in asymptomatic patients in the general population.

Methods:

For this review I am focusing on 2 key questions (KQ). KQ1: What is the accuracy of auscultation for carotid bruit to predict fatal or nonfatal ischemic stroke or TIA? KQ2: What is the accuracy of auscultation for carotid bruit to detect potentially clinically important CAS (60% to 99%)? This review is an adjunct to a review by the USPSTF to update their previous 1996 and 2007 reviews of screening for Carotid Artery Stenosis (CAS). This focuses on auscultation for carotid bruit as the screening test with angiography as the confirmatory testing. An analytic framework was developed for this review following USPSTF methods and is shown in Figure 2.

- KQ1: What is the accuracy of auscultation for carotid bruit to predict fatal or nonfatal ischemic stroke or TIA?
- KQ2: What is the accuracy of auscultation for carotid bruit to detect potentially clinically important CAS (60% to 99%)?

Figure 2. Analytic Framework for Screening for Carotid Artery Stenosis



KQ = Key Question; CAS = carotid artery stenosis; CEA = carotid endarterectomy

Study Inclusion/Exclusion Criteria

For the purposes of this review I defined clinically significant CAS to be 60-99 percent because this is the cutoff generally used to justify use of carotid endarterectomy or carotid artery stenting and is consistent with that used in the ACAS trial published in 1995 and ACST trial in 2004. However, I will not exclude studies looking at 50 percent or greater to ensure that studies using such a cutoff that may provide valuable accuracy information are not missed. For inclusion in this review, studies had to look at populations of adults who were asymptomatic for any stroke symptoms and are screened for CAS by auscultation for carotid bruit. Asymptomatic must indicate that these patients have no significant neurologic symptoms that are referable to the carotid artery and also no previous strokes or TIAs. Patients must also lack a history of previous myocardial infarctions as this is a sign of poor cardiovascular health and likely delineates a subgroup of higher risk patients that is not representative of the asymptomatic general population. Adults are considered to be people 19 years of age or older. This excludes children and adolescents and patients that do not speak English. Also it excludes any patients currently suffering from neurologic symptoms or those with a history of TIAs or stroke. I'm also excluding any patients undergoing coronary artery bypass graft (CABG) procedures and those who have received remote procedures for treatment of CAS such as CEA or CAAS and are undergoing surveillance for recurrent problems as these patients are not considered asymptomatic.

Relevant studies must compare this included population of patients undergoing screening to a group of patients with similar characteristics who are not screened by auscultation for carotid bruit or not found to have a bruit on auscultation. The intervention of auscultation for carotid bruit must be performed by primary care physicians in an office setting as this is generally considered to be the most useful setting for this screening technique. This includes

cardiologists and neurologists but excludes studies examining carotid auscultation by vascular surgeons as they are considered more highly specialized than other physicians generally practicing in primary care settings. For inclusion the studies must be RCTs or cohort studies comparing screened versus non-screened group. For the other KQ studies must be diagnostic accuracy studies also evaluating auscultation for bruit with comparison to the gold standard of angiography. They must be published since 1996 since this is when the last USPSTF review examining the topic of auscultation for carotid bruit was completed. All other study types are excluded, including case-control studies to avoid introducing further bias including confounding, measurement, and selection bias (37). To better ensure that studies were performed in populations generalizable to the U.S., I am including only those performed in countries with a "very high" human development index based on the UN Development Program. This comprises 47 countries. The predetermined inclusion and exclusion criteria are included in a PICOTTS table shown in Table 1.

Table 1. PICOTTS Table

	Inclusion	**Exclusion**
Populations	Adults in the general population asymptomatic for stroke symptoms who are screened for CAS by auscultation for carotid bruit. Asymptomatic indicates they have no significant neurologic symptoms referable to the carotid artery and have no previous cerebrovascular events. Adults defined as 19 years or older.	Children and adolescents; symptomatic adults with CAS or with history of TIAs, strokes, or MI. People with remote CEA or CAAS for previous stenosis undergoing surveillance. Also patients undergoing CABG or myocardial revascularization.
Intervention	Auscultation for carotid bruit by primary care physicians in office setting as screening tool for clinically important CAS necessitating referral for duplex ultrasonography. Include cardiologists and neurologists in clinic setting.	Auscultation by vascular surgeons

Comparison Group	Adults in the general population asymptomatic for stroke symptoms who are NOT screened for CAS by auscultation for carotid bruit or who are found to not have bruit on auscultation.	
Outcomes	1. Fatal or nonfatal ischemic stroke or TIA 2. Carotid Artery Stenosis	
Time for Intervention to Work	Follow-up of at least 24 months for stroke and/or TIA.	
Time period for relevant studies/literature	Studies published since 1996 (year of previous USPSTF review examining auscultation for Carotid Bruit)	Anything prior to 1996
Setting	Studies conducted in developed countries defined as those with a "very high" human development index per the UN Development Program. (47 countries) http://hdr.undp.org/en/media/HDR_2011_EN_Table1.pdf	All other countries
Study Designs	RCTs or cohort studies comparing screened vs. non-screened groups; diagnostic accuracy studies that compared screening tests to *gold standard(angiography)* to evaluate effectiveness	All other designs

Data Sources and Searches

The latest review examining the topic of screening for carotid bruit was conducted in 1996. To ensure that I examined the updated literature since this review, I searched the MEDLINE literature for articles that were written in English that addressed my KQs. I looked for RCTs and cohort studies comparing screening for carotid bruit in asymptomatic adults to those not screened for carotid bruit or those found to possess a bruit compared to those without. I also searched for diagnostic accuracy studies comparing auscultation for carotid bruit to the reference standard of angiography. For the MEDLINE search I used the focused MeSH terms "Carotid Artery Stenosis," "Carotid Artery Diseases," and "bruit" yielding 216 results. I utilized the filters "Humans," "English," "Adult: 19+ years," and also filtered by study type. This narrowed the results to 128 studies. Narrowing further to include only studies published since 1996 limited this to 87 studies. I also augmented this search by hand-searching the reference lists of several relevant studies and review articles to find any other studies that met the inclusion criteria.

Study Selection

I selected and reviewed the titles and abstracts of the articles that were retrieved for my KQ in a systematic manner using one reviewer. I utilized predetermined inclusion and exclusion criteria that were similar to those used in previous USPSTF reviews and are included in Table 1. For all included articles I then pulled the full texts and reviewed them based on the previously specified inclusion/exclusion criteria to ensure that they still met these criteria to be included. If not they were excluded as well. I identified one additional study that met inclusion criteria through my hand search of the reference lists of several relevant articles. To be included the studies had to be RCTs or cohort studies of asymptomatic patients at least 19 years of age, from which data on cerebrovascular outcomes could be extracted for KQ1. They could also be diagnostic accuracy studies comparing auscultation for carotid bruit to the gold standard of angiography in asymptomatic patients at least 19 years of age for KQ2. These studies had to be published in English. The study selection was done using a single reviewer method but would have entailed dual-review if more time and resources were available.

Data Extraction and Quality Assessment

I reviewed the full-text articles for all the citations meeting the eligibility criteria and quality-rated them independently using a single reviewer method. Again, for the purpose of this review a single reviewer was sufficient. However, double review would have been utilized if more time and resources were available. Data extracted from the studies included the source population and comparison group(s); average age; sample size; average time of follow-up; sensitivity, specificity, and accuracy of detecting stroke, TIA, and stroke death; false-positive and false-negative rates; gold standard utilized for stenosis measurement; and overall conclusions from the studies. This extracted data is included in Table 2.

I attempted to follow the defined criteria specified in the USPSTF procedure manual to evaluate internal and external validity of the included studies and literature sources and apply a modified scoring method to grade the criteria for each study (38). For this grading I gave a score of 1-, 2-, or 3-plus (+) to each criteria of the study with 3-plus being the best or most positive rating. An overall quality assessment was formulated that takes into account the scoring for each criterion. Using this grading method, I evaluated the quality of RCTs and cohort studies based on the assembly and maintenance of comparable groups; level of differential and overall follow-up of subjects; equal, valid, reliable, and appropriate outcome measures; clearly defined screening/interventions; generalizability; and the validity of their conclusions. I evaluated diagnostic accuracy studies based on the adequate description of the screening test, use of a credible reference test, independent interpretation of the reference, handling of indeterminate results, sample size and spectrum of patients, generalizability, and the validity of their conclusions. These studies were all given a rating of "good," "fair," or "poor" based on the criteria presented in the USPSTF procedure manual and the definitions for these ratings which are also published (38). For the strength of evidence assessment I took into account both the certainty and the magnitude of effect for the results and conclusions from the included articles and rated it as either low, moderate, or high. I organized this information into a quality and strength of evidence table and it is displayed in Table 3.

Data Synthesis and Analysis

I compiled all of the relevant data from the included studies quantitatively and qualitatively in a table and in narrative format. This is shown in Table 2. I organized the synthesized data for KQ1: What is the accuracy of auscultation for carotid bruit to predict fatal or nonfatal ischemic stroke or TIA? I also did this for the KQ2: What is the accuracy of auscultation for carotid bruit to detect potentially clinically important CAS (60% to 99%)? I grouped the data by

those screened for bruit vs. not screened when applicable or by those found to have bruit vs. those without bruit.

Role of Funding Source(s)

I did not receive any specified funding for this particular review and there are no known conflicts of interest related to this.

Table 2. Data Extraction Table

KQ1:

Study Reference	Study Design	Source Population & Comparison Groups	Sample Size & Avg. Age	Mean Follow-up time	Sensitivity, Specificity, & Accuracy for stroke	False Positive & Negative Rate for Stroke	Sensitivity, Specificity, & Accuracy for TIA	Sensitivity, Specificity, & Accuracy for stroke death	Overall Conclusion(s)
Gillett (2003)	Prospective Cohort (The Fremantle Diabetes Study)	Australian community-based sample of patients w/ type 2 diabetes and no hx of cerebrovascular disease; Comparison of those with carotid bruit to those without bruit.	1181 patients; 64 years	6.5 years; 7676.5 patient-years (344.5 w/ bruit; 7332 without bruit)**calculated using mean follow-up time of 6.5 years and sample size.*	Sens: 13.4%; Spec: 96.7%; Accy: 87.2%	FP: 3.3%; FN: 86.6%	NR	NR (25 stroke deaths during follow-up but not reported by bruit status)	Type 2 diabetic patients w/ incidental carotid bruits have > 6 times risk of first stroke in first 2 years compared to those without bruit and should receive intensified management of vascular risk factors. No difference in risk beyond initial 2 year period.

Shorr (1998)	Prospective Cohort (SHEP study)	Asymptomatic Cohort from SHEP study ≥ 60 years old w/ avg BP of 160-220/<90 mm Hg. Comparison of those w/ Bruit to those w/out Bruit.	4,442 patients; 71.5 years	4.5 years; 18,488 patient-years	Sens: 9.1%; Spec: 93.75%; Accy: 89.4%	FP: 6.25% FN: 90.9%	NR	NR	Carotid bruits in asymptomatic elderly patients w/ isolated systolic hypertension do not identify persons at greater risk of stroke. Small trend toward increased risk in patients aged 60-69 years but not aged ≥70 years

KQ2:

Study Reference	Study Design	Sample Size & Avg. Age	Degree of Stenosis	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Overall Accuracy (95% CI)	Overall Conclusion
NA	*	*	*	*	*	*	*	*	*

Table 3. Quality & Strength of Evidence Table

	RCTs and Cohort Studies								
Study	Assembly of Comparable Groups & Consideration of Confounders	Maintenance of Comparable Groups	Significant Loss to Follow-up	Measurements Equal, Valid, & Reliable	Clear definition of Screening tool used	Considers Relevant Outcomes (Stroke/TIA)	Generalizability	Strength of Evidence (High, Moderate, Low)	Quality (Good, Fair, Poor)
Gillett (2003)	++	++	+++	+++	++	++	++	Moderate	Good
Shorr (1998)	++	+++	+++	++	++	++	++	Low	Fair

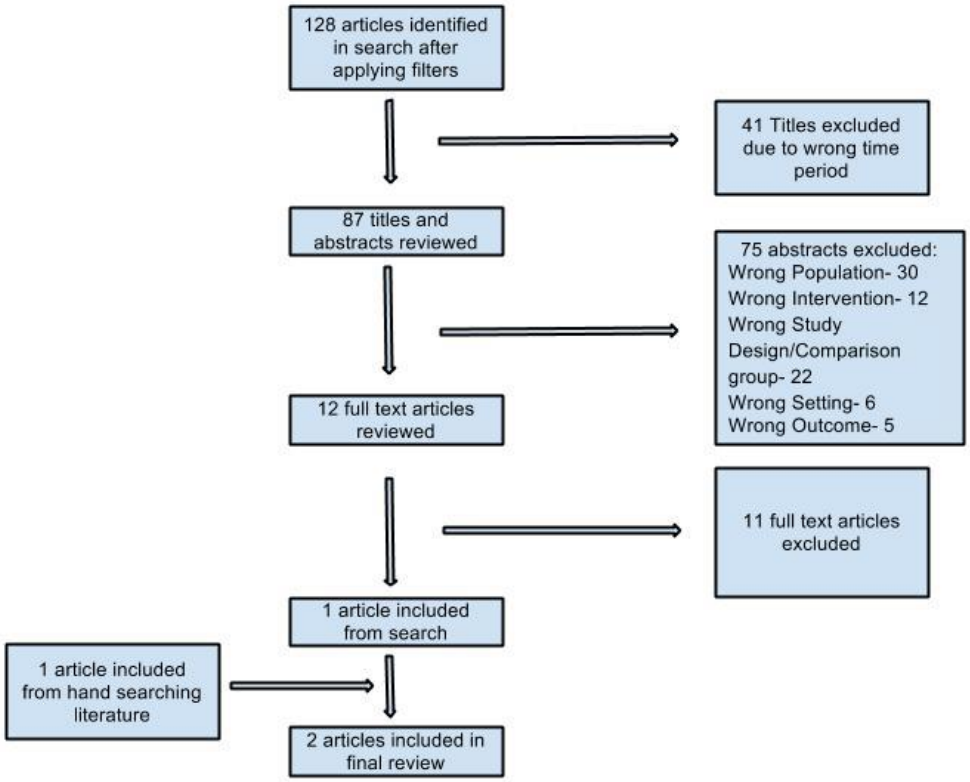
	Diagnostic Accuracy Studies							
Study	Screening Test Adequately Described	Credible Reference Standard used	Reference Standard Interpreted Independently	Handling of Indeterminate Results	Sample Size & Spectrum of Patients	Generalizability	Strength of Evidence	Quality
N/A	*	*	*	*	*	*	*	*

Results:

Search Results

The initial MEDLINE search yielded 216 results. After applying the filters "Humans," "English," "Adult: 19+ years," and also filtering by study type, this left me with 128 results. Out of these, 87 articles were published within the target time frame of 1996 to present. Through title and abstract review of these articles, I selected 12 articles for full-text review. At the full-text review stage I excluded 11 of these articles, mostly due to wrong population, wrong intervention, wrong comparison group, or wrong outcomes reported. I identified one additional article for inclusion through hand-searching the reference lists of other relevant articles, thus resulting in 2 articles for inclusion for KQ1. The study selection strategy used is demonstrated with a flow chart shown in figure 3.

Figure 3. Search Inclusion/Exclusion Flowchart



There were no RCTs meeting inclusion for KQ1 that directly compare a cohort of patients screened for carotid bruit to those not screened. One good quality and one fair quality prospective cohort study were included comparing patients with and without carotid bruit. One fair to good quality systematic review/meta-analysis was also identified that evaluated a subset of studies directly comparing outcomes in patients with a carotid bruit to those of patients found to lack a carotid bruit after screening by auscultation. This systematic review includes in its analysis the 2 cohort studies that met my inclusion criteria. Due to this it is not included in my analysis, but the findings are discussed in the discussion section.

There were no included studies for KQ2 as I was unable to identify any meeting criteria that used angiography as the gold standard for measurement of degree of stenosis. Because of this, I went back and identified studies from my search that met inclusion except for their use of duplex ultrasound instead of angiography as the reference standard. Based on this, I identified 2 studies and a systematic review for discussion of KQ2. Because these studies did not originally meet inclusion criteria, I excluded them from any formal analysis for KQ2 but discussed their results in the discussion section, similar to the approach taken for the systematic review for KQ1.

Summary of Study Results

Key Question 1: What is the accuracy of auscultation for carotid bruit to predict fatal or nonfatal ischemic stroke or TIA?

Two prospective cohort studies were identified and included for KQ1 that provided data on the accuracy of auscultation for carotid bruit for predicting ischemic stroke. Neither of these studies reported data for TIA or stroke death that could be used to calculate sensitivity, specificity, or overall accuracy for these events/outcomes. These two studies of fair to good quality for KQ1 provide a sensitivity range of 9.1%-13.4% and a specificity range of 93.75%-96.7% (32, 39). Crudely averaging the values from these studies gives a sensitivity of 11.25%

and specificity of 95.2% for the accuracy of auscultation for carotid bruit to predict future stroke based on bruit status.

The first study, Gillett et al. published in 2003, looked at a subset of 1181 patients from the Fremantle Diabetes Study which used a community-based sample of 1294 patients in Western Australia with type-2 diabetes and no history of cerebrovascular disease (39). The average age of the study patients was 64 years and the mean follow-up time was 6.5 years or 7676.5 patient-years. The study compared the patients in the community cohort found to have a carotid bruit to those without a carotid bruit. Based on the data provided, I was able to calculate sensitivities, specificities, and accuracy for predicting those who will suffer a stroke over an average of 6.5 years. I also used this to calculate prevalence of stroke in the population, positive predictive value, negative predictive value, false-positive rate, and false-negative rate. The sensitivity, specificity, and accuracy of auscultation for carotid bruit to predict stroke were 13.4%, 96.7%, and 87.2% respectively (39). There were 134 first strokes during follow-up with 18 in patients with carotid bruit and 116 in those without. Of those patients who did not suffer a stroke, 35 possessed a bruit and 1012 did not. The prevalence of stroke in the study participants was 11.3%. Positive and negative predictive values were 34% and 89.7%, while the false-positive and false-negative rates were 3.3% and 86.6% respectively (39). Data for the outcome of TIA was not reported. Also the authors state that 25 stroke deaths occurred during follow-up but they do not report this outcome by carotid bruit status. Thus relevant accuracy data for this outcome could not be determined. The authors concluded that type 2 diabetic patients who are found to have incidental carotid bruits have more than six times the risk of suffering a first stroke in the first two years of detection compared to those without a carotid bruit and they should

receive more intensified management of vascular risk factors. Beyond the initial two year period they found no difference in risk between these groups (39).

The other included study, Shorr et al. published in 1998, looked at a subset of 4442 patients from the original 4736 participants in the Systolic Hypertension in the Elderly Program (SHEP) who had no history of cerebrovascular disease symptoms or myocardial infarction (32). All of these patients were at least 60 years old with isolated systolic hypertension, having an average blood pressure of 160-220/<90 mm Hg. The average age of included patients was 71.5 years and the mean follow-up time was 4.5 years or 18,488 patient-years. Like the other included study, this one compared a cohort of patients with a carotid bruit to those without a bruit. Over an average follow-up time of 4.5 years the calculated sensitivity, specificity, and accuracy of auscultation for carotid bruit to predict stroke were 9.1%, 93.75%, and 89.4% respectively (32). During follow-up 231 strokes occurred, 21 of which happened in patients with a carotid bruit and 210 in those without a bruit. Out of the patients who did not suffer a stroke, 263 possessed a carotid bruit compared to 3948 without bruit. The prevalence of stroke was 5.2% with positive and negative predictive values of 7.4% and 94.9% respectively. There was a false-positive rate of 6.25% and false-negative rate of 90.9% (32). This study, like the other one, did not report similar data for the outcomes of TIA and stroke death and thus the accuracy for these other outcomes remains unclear based on this more recent evidence. The authors of this study concluded that carotid bruits found in asymptomatic elderly patients with isolated systolic hypertension do not identify persons at greater risk of stroke. They did note a small trend toward increased risk in patients of age 60-69 years but not in those at least 70 years old (32).

The systematic review/meta-analysis I identified for KQ1 was published in 2010 and it included 28 prospective cohort studies following a total of 17,913 patients for 67,708 patient-

years (40). The mean age of patients was 64.8 years with a range of 60 to 71.6 years. The authors looked at the relevant outcomes of TIA, stroke, and stroke death and limited their inclusion criteria to prospective cohort studies performed in asymptomatic adults (40). However, they did not provide data in terms of sensitivity, specificity, and overall accuracy. Instead the authors provided pooled rate ratios for those with carotid bruits compared to those without. There were 5 studies that investigated the outcome of TIA and provided head-to-head comparisons for those with and without bruits. The pooled risk ratio for suffering a TIA in patients with carotid bruit compared to those without was 4.00 (1.77-9.03). There were 6 studies providing direct comparison of these two patient groups for the outcome of stroke. The pooled risk ratio for suffering a stroke was 2.49 (1.77-3.52). This pooled data took into account the two included studies for KQ1 of my current review which gave stroke rate ratios of 3.18 and 1.46 respectively (32, 39). For stroke death there were 3 studies that provided direct comparison of the two patient groups giving a pooled risk ratio of 2.71 (1.33-5.53). The authors of this review/meta-analysis concluded that patients who possess a carotid bruit have more than 4 times the risk of TIA and more than 2 times the risk of stroke and death from stroke compared to patient controls without carotid bruits (40).

Key Question 2: What is the accuracy of auscultation for carotid bruit to detect potentially clinically important CAS (60% to 99%)?

There were no studies found that addressed this question using the proper gold standard of angiography. However, I identified 2 cohort studies that would have otherwise met inclusion as well as a systematic review that all use the gold standard of duplex ultrasound to look at this question. The findings and conclusions of these studies, though not included for formal analysis of KQ2, are presented here and further examined in the discussion section.

The first cohort study, published in 2009, looked at a subset of multiethnic community-based patients from the Northern Manhattan Study (NOMAS) who were asymptomatic and with no history of cerebrovascular disease (41). This entailed 686 of the original 3298 NOMAS patients making up the stroke-free cohort who were auscultated for carotid bruit by neurologists and also received duplex ultrasonography of the carotid arteries. Approximately 9% of these patients or 61 had a history of coronary artery disease which was defined as a prior history of MI, CABG, or angioplasty (41). These patients were not separated out in the analysis, but because they made up such a small percentage of the included patients, the data is still mostly representative of asymptomatic patients as defined by my inclusion criteria. The average age of the included patients was 68.2 years with a range of 40-96 years. The racial make-up was 58% Hispanic, 21% African-American, and 19% Caucasian. Both carotid artery sides were examined for each patient accounting for 1372 arteries for analysis. A carotid bruit was detected in 28 subjects with 8 being bilateral, thus accounting for 36 arteries with bruits while 1336 were without bruit (41). The prevalence of bruit in the study population was 4.1% and that of CAS $\geq$ 60% detected by duplex ultrasound was 2.2%. The sensitivity, specificity, and accuracy of auscultation for carotid bruit to detect ipsilateral CAS $\geq$ 60% were 56.25%, 98%, and 97.5% respectively. The positive and negative predictive values were 25% and 99%, while the false-positive and false-negative rates were 2% and 43.75% respectively (41). The authors concluded that a carotid bruit heard on physical exam should prompt further evaluation with carotid duplex ultrasound; however, with its low sensitivity and positive predictive value combined with its false-negative rate, bruit auscultation is not adequate for excluding CAS $\geq$ 60% (41).

The other cohort study using ultrasound as the reference standard was published in 2007 and investigated the accuracy of the screening physical exam to identify CAS in a subset of

asymptomatic French patients from the Evaluation du Dépistage de la Coronaropathie (EVADEC) study (42). This study looked at 2736 asymptomatic French patients with a mean age of 52.3 years and a range of 20-90 years. The authors were investigating not only carotid bruits and their ability to identify CAS but also femoral bruit and its ability to identify femoral plaque and lower limb atherosclerosis as physicians in practice usually auscultate and palpate both of these arteries to assess atherosclerosis during a full vascular physical exam. For CAS accuracy determination the study used CAS > 50% identified on ultrasound as its cutoff. There were 106 patients with carotid bruits in the study population giving a prevalence of 3.9%. The prevalence of CAS > 50% in the population was 4.2% as 114 patients were found to possess this (42). Sensitivity, specificity, and accuracy measures were not provided from this study, yet it does provide positive and negative likelihood ratio calculations (LR+ & -) for the ability of auscultation for carotid bruit to detect ipsilateral CAS > 50%. The necessary data to calculate sensitivity, specificity, and accuracy were not provided within the study, specifically the numbers of patients with and without bruits who possessed or did not possess CAS > 50%. However, the LRs include sensitivity and specificity in their calculation and thus can be considered meaningful data for investigation of accuracy. The LR+ and 95% confidence interval for detection of carotid bruit in patients with ipsilateral CAS > 50% was 0.90 (0.34-2.41). The LR– and 95% confidence interval was 1.00 (0.97-1.04) (42). The authors concluded that the presence of a carotid bruit did not affect the likelihood of carotid stenosis and carotid auscultation does not seem to provide strong predictive information on underlying atherosclerosis (42).

I identified one recent systematic review/meta-analysis published in 2012 that also attempted to evaluate the accuracy of carotid bruit to detect various levels of CAS (43). The

meta-analysis included 26 studies looking at a total of 15,117 carotid arteries, 3502 with bruits and 11,615 without bruits (43). In the meta-analysis they classified degree of stenosis into several categories. A total of 12 studies in the analysis looked at CAS ≥ 50% for a pooled sensitivity and specificity of 55.8% and 82% respectively. The false-positive and negative rates are 18% and 44.2%. There were 7 studies that used a CAS cutoff of ≥ 60% and they yielded a pooled sensitivity and specificity of 57.5% and 80% respectively. The false-positive and negative rates were 20% and 42.5% respectively. For CAS ≥ 70% there were 6 studies giving a pooled sensitivity and specificity of 43.9% and 86% respectively with false-positive and negative rates of 14% and 56.1% (43). Finally the authors defined a group as clinically relevant stenosis which included CAS ≥ 70%, ≥ 75%, and ≥ 80%. A total of 12 studies looked at this category giving a pooled sensitivity and specificity of 53% and 83% respectively with false-positive and negative rates of 17% and 47% (43). The authors concluded that routine examination for carotid bruit in clinical practice is of moderate value for detecting CAS as it has high specificity but low sensitivity. The absence of bruit cannot reliably rule out the presence of CAS (43).

Discussion:

In the last evidence review and recommendation update by the USPSTF analyzing auscultation for carotid bruit as a CAS screening tool in 1996, they determined that there was insufficient evidence to recommend for or against screening asymptomatic people for CAS using this means during physical exam (10). This was based on current evidence at the time that risk of major stroke in asymptomatic patients due to CAS is low without surgery at approximately 1% per year, there was small absolute risk reduction in stroke and death from surgery over 5 years in the ACAS, and the fact that the low complication rates of surgeons in the ACAS of < 3% are unlikely to be representative of rates for endarterectomy performed in the community setting

(10). Therefore it could not be determined if the benefits outweigh the risks for widespread screening. In their review they also looked at the accuracy of auscultation for bruit in identifying clinically significant CAS. Using the reference standard of 70-99% stenosis on carotid angiogram, the sensitivity and specificity of a carotid bruit was determined to be 63-76% and 61-76% respectively (10, 44). Comparatively, duplex ultrasound was found to have a sensitivity of 83-86% and specificity of 89-94% (10, 45) They did not provide sensitivity and specificity measures for the ability of auscultation for carotid bruit to determine those asymptomatic patients with no previous stroke or TIA who will suffer a stroke or cerebrovascular outcome, but found the annual incidence of stroke ipsilateral to bruit to be 1-3% in these patients (10, 31, 35, 46).

Since the publication of the 1996 recommendation as well as the 2007 update, very few studies have been published that investigate the accuracy of auscultation for carotid bruit as a screening tool for predicting stroke outcomes as well as clinically significant CAS in asymptomatic patients utilizing a reference standard of angiography. For KQ1 the 2 included studies provided a sensitivity range of 9.1%-13.4% and a specificity range of 93.75%-96.7% or a crude average of 11.25% and 95.2% respectively for identifying stroke while that for the outcomes of TIA and stroke death remains unclear (32, 39). The systematic review for KQ1 contributed nothing more to these accuracy measures but found that patients with carotid bruits have 4 times the pooled risk of TIA and over 2 times the risk for both stroke and stroke death compared to those lacking bruits (40).

For KQ2 there were no studies that originally met inclusion, yet two cohort studies and a systematic review on the topic using duplex ultrasound as the reference standard were identified for discussion. These studies show that, though the specificity is reasonably higher compared to

the sensitivity values of auscultation for bruit with a range of 80-98% versus 56.25-57.5% for CAS ≥ 60%, both the sensitivity and specificity are poor and not adequate for a screening test. The LRs for identifying CAS ≥ 50% with this test were also both very close to 1, indicating that the test results show little to no association with CAS.

The most significant weaknesses and limitations of my study arise from those of the included studies themselves and the subsequent level of certainty of my results. Because my results were based on so few studies, most of which were graded as fair quality, the level of certainty for my findings is low to fair at best. For KQ1, both the cohort studies did a fair job compiling and maintaining comparable groups, though some differences did exist between those with bruits compared to those lacking them. These included slightly older age, higher total cholesterol, increased systolic BP, and higher rates of hypertension in those with bruits for both of the studies. This leaves potential for confounding due to more poor health states in the bruit groups. I deemed the strength of evidence to be low to moderate at most. This was mostly related to the level of certainty of the accuracy measures as the studies themselves did not provide sensitivity and specificity values. Instead, I attempted to calculate these by hand using relevant pieces of data within the study. These values could differ to some degree if there is other necessary data that was not included or clearly denoted within the published studies themselves. Also they did not provide evidence for the outcome of TIA in addition to stroke, which further limits the strength of evidence for my KQ. Additionally, generalizing the results to a largely healthy asymptomatic population is somewhat problematic because of the study populations used in both of these studies. All of the patients in the first study were type-2 diabetics while those in the other study were all non-institutionalized elderly at least 60 years old with isolated systolic hypertension (32, 39). In the Shorr et al. study the population was a highly selected one of

elderly hypertensive patients representing only 1% of those initially screened making generalizability of the findings even to other elderly hypertensive populations somewhat precarious. As diabetes, increased age, and hypertension have all been linked to increased risk for CAS and subsequently stroke, studying the accuracy of a screening test to identify these outcomes in populations solely made up of patients with these risk factors may actually confound the results due to a greater number of CAS cases and stroke outcomes occurring in these populations (25, 27).

In the systematic review/meta-analysis identified for KQ1 several of the included studies were not very recent, with years dating back to the late ‘70s and early ‘80s. The results from these older studies could bias the rate results of the pooled analysis for relevant outcomes as it is likely that more recent changes in medical management may have altered the prognosis of patients with bruits. The inclusion of these less recent studies was the most limiting factor affecting the quality of this review. There was also a high amount of heterogeneity between the studies and their results, especially in terms of the included study populations and reporting of potential confounding factors such as prevalence of hypertension or diabetes between groups (40). Though this study’s results provide fair evidence that patients found to possess carotid bruits are at greater risk of suffering poor cerebrovascular outcomes than those lacking bruits, this tells us little about how accurate auscultation for carotid bruit is as a screening test to detect those who will suffer these bad cerebrovascular outcomes.

For KQ2 the greatest weakness in all of the studies comes from their use of duplex ultrasound as the reference standard for stenosis calculations instead of the true gold standard of angiography which is a much more accurate test for identifying degree of stenosis. However, the risk of harmful outcomes such as stroke that arise from invasive testing like angiography makes

it difficult to ethically subject such asymptomatic patients to this invasive testing. The use of non-invasive tests like ultrasound which have very little risk of harmful outcomes from the testing itself are much easier to justify in such studies and still provide meaningful data on the accuracy of carotid bruits for identifying significant degrees of CAS.

The two cohort studies were graded good and fair quality respectively while the systematic review was poor. The Ratchford et al. study provided comparable groups of patients with and without bruits with the most significant difference arising in average age of the groups. That of patients with bruits was higher at 75.1 years compared to 67.9 years for those without bruit (41). The fair quality cohort study by Cournot et al., unlike the other study, did not provide comparable groups separated by carotid bruit status. Instead they grouped patients by having a normal versus abnormal vascular physical examination that took into account not only presence or absence of carotid bruits but also presence or absence of various lower limb pulses. They also did not provide a distribution of various risk factors such as smoking and diabetes by groups of patients with carotid bruits versus those without. Therefore it is difficult to assess the potential for confounding from these variables. In the same study the vascular physical exam was performed in all patients by one specially trained study physician who was a preventive cardiologist. Because the study physician was specially trained in auscultation of carotid bruit for this study, the ability of this physician to detect bruit compared to that of physicians in an average community primary care setting may be different. Thus this could affect the generalizability of this study to the community setting, although likely very minimally. Though the first cohort study's results are generalizable to other multiethnic community populations in the US as Manhattan provides a very diverse, yet representative subset of the country's general population make-up, the generalizability of the Cournot et al. study to a US community is likely

lower as it was carried out only in French patients. Though this study considers the relevant outcome of CAS > 50% ipsilateral to carotid bruit, it would have provided a much better assessment of accuracy if they included sensitivity and specificity calculations based on bruit status instead of solely giving likelihood ratios. Also these numbers would have been much easier to compare across other studies as these are the most commonly used measures to assess accuracy of screening tests (47).

The systematic review by McColgan et al. for KQ2 was poor, mostly due to the fact that the included studies did not limit their populations to only asymptomatic patients. Instead they included all populations of patients such as those with coronary artery diseases or those scheduled to undergo CABG. Very few of the included studies only looked at asymptomatic patients. This makes it quite difficult to generalize their findings and conclusions to an asymptomatic population with no previous history of poor cerebrovascular/cardiovascular outcomes. Also, like the review for KQ1, several of the included studies are not recent and the data is likely outdated to some degree: one of the studies dates back to 1975 and most of the others were published in the 1980s to early 1990s. The authors actually reported study quality as weak in 22 of the included 26 studies, mostly because of lack of blinding and potential for publication bias (43). There was significant heterogeneity between the included studies for all the categories of CAS including wide variation in the imaging techniques used to assess degree of CAS. Only one study actually reported using NASCET or ESCT criteria to define stenosis and this study was carried out in patients scheduled for coronary artery bypass (48). It was also carried out in a country that does not meet the setting criteria for this review, further affecting generalizability. Finally, they looked at 12 studies investigating their category of clinically relevant stenosis (≥70%, ≥75%, and ≥80%). However, only 2 of these 12 studies investigated

asymptomatic bruits and subgroup analysis for asymptomatic bruits was not performed due to the low number of studies (43). Again this greatly brings into question the validity and generalizability of these results for an asymptomatic population.

For KQ1, although the specificity determined from the two cohort studies seems to be a high value as it sits above the 90% threshold, specificities for screening tests must generally be 98-99% to be considered adequately accurate (47). When screening a population the expectation is generally that the prevalence of what you're screening for is low and that the vast majority of people screened will not possess the disorder in question. So by only identifying 95% of this huge number of people who do not have the disorder, you are still left with the remaining 5%. Subsequently 5% of this huge number is still a huge number thus leaving you with a ton of false-positive results. Therefore this specificity falls short and the sensitivity is also very low for identifying the outcome of stroke. These values are certainly not adequate for a screening test. Such a test would lead to false-positives nearly 5% of the time and would produce a false-negative result nearly 89% of the time. Based on this, screening for carotid bruit would falsely identify many patients believed to be at greater risk for stroke who actually are not and also fail to identify a huge amount of patients who will go on to suffer a stroke over the next 5.5 years approximately. If the aim of a CAS screening test is to accurately identify those at increased risk of future stroke in order to prevent this outcome, the use of auscultation for carotid bruit would present much difficulty in sufficiently satisfying this objective.

Though the cohort studies for discussion of KQ2 provide different measures of accuracy in their use of sensitivity and specificity versus likelihood ratios and use different CAS cutoff points, in combination with the systematic review they point to similar conclusions with regard to accuracy of auscultation for carotid bruit as a screening test. Based on the results, both the

sensitivity and specificity are poor and not adequate for a screening test as was the case for KQ1. These accuracy values lead to a very weak ability to rule out as well as rule in clinically significant CAS ≥ 60% with tests yielding false-negative results more than 40% of the time and false-positive results as much as 20% of the time. This would cause a substantial amount of screened people to not receive confirmatory testing and potentially necessary treatment for CAS that they are made to believe they do not possess based on the wrong results from their screening test. A portion of these patients would suffer strokes or TIAs that could have been avoided had they received proper preventative treatment such as CEA or CAAS. On the other side of this scenario screening would also cause a considerable amount of people to be subjected to further confirmatory testing that may be harmful, anxiety, and even unnecessary and harmful treatment for CAS that was actually not present.

Also the LRs for identifying CAS ≥ 50% with this test were both very close to 1, indicating that the test results show little to no association with CAS. Thus the test as a screening tool would not yield a significant difference between the pre-test and post-test probabilities of CAS and should have little effect on clinical decision making, especially in the case of a negative test result. Because these studies rely on the use of an imperfect reference standard in duplex ultrasound, the accuracy measures may actually be underestimated compared to the true accuracy of the test. However, based on the results of two meta-analyses examining the accuracy of ultrasound compared to angiography, it seems very unlikely that the use of ultrasound as a reference would account for more than just a slight difference of a few percentage points in accuracy measurements (49, 50). Therefore, I would expect any underestimation to only be to a small degree and not account for a large enough difference in sensitivity to change the conclusion about the accuracy of auscultation for carotid bruit. Therefore the implications from

the studies for both KQ1 and KQ2 are that auscultation for carotid bruit has less than adequate accuracy as a screening test for CAS and stroke outcomes and should not be used for this purpose when just considering its accuracy. However, it is important to keep in mind that the level of certainty of the findings is only fair at best.

Yet when determining whether a test should be used for screening, sensitivity and specificity are not the only aspects that are important for consideration. This is especially the case when screening for specific levels of CAS. Sensitivity and specificity only tells us how much CAS we can find and whether or not we are labeling too many people through false-positives or negatives. However, they don't tell us if we're finding the right people that we are looking for. What we are most concerned with is preventing stroke outcomes in patients with CAS and these depend on much more than solely the level of CAS a patient possesses. Clearly all patients who possess CAS $\geq$ 60% do not suffer a stroke and experiencing this outcome depends on whether the carotid plaque is unstable and ruptures and also on a multitude of other risk factors specific to the patient. We need to better understand which patients with CAS $\geq$ 60% will go on to suffer a stroke. What we would really like to have is a reliable means to risk stratify these patients in the general population and separate out only those for screening who are most likely to suffer stroke outcomes from CAS. In this scenario, the sensitivity and specificity values may actually be adequate because we could be somewhat certain that we are screening the right people, those most likely to be affected by stroke from CAS. Unfortunately we are currently unable to do this in a reliable manner using available risk assessment tools. Until such risk stratification is available we must consider screening in the entire general population. This review shows, with only fair certainty, that such screening is inaccurate.

However, this analysis evaluating the accuracy of this specific screening test only represents the first step in evaluation of an entire screening program for CAS. Though the results of this review show me with fair certainty that this individual test may be inaccurate for identifying clinically significant CAS and strokes in the general asymptomatic population, further investigation remains to be done to fully elucidate the usefulness of this specific screening test for identifying bruits within the greater screening program for CAS. As past studies have alluded to, it may even be that assessing for carotid bruits is most useful for determining general atherosclerotic burden in a patient that could lead to various other poor cardiovascular outcomes beyond stroke, such as myocardial infarction (7, 9, 39). Though screening for bruits in this context may not lead to reduced strokes, it may serve as a tool for physicians to better assess their patient's cardiovascular risk level in general. However, this still remains to be shown with strong certainty.

Research Gaps & Future Directions

The most obvious gap in research pertaining to the topic of screening for CAS using auscultation for carotid bruit is the lack of any RCTs directly comparing a cohort of patients screened for carotid bruit to those not screened to determine if this results in reduced cerebrovascular outcomes. These high-quality study types provide much better linkages to causation and also are less vulnerable to potential biases that arise due to lack of blinding of information from both researchers and patients throughout the study (51). Future RCTs investigating screening for CAS could take us beyond just accuracy of auscultation for bruit as a screening test. These studies could help give meaningful conclusions about whether screening for CAS in this way actually causes lower rates of stroke and stroke outcomes in the population. Yet this specific screening test is only the initial step in a whole screening program that

encompasses a treatment protocol. This ultimately leads to CEA or CAAS to prevent stroke as shown in figure 2. The evidence on benefits as well as risks of harm from these treatments is still very uncertain in the general community. In the future we must continue to better delineate these risks to fully understand the benefit that can arise through screening for CAS.

Also future studies examining the accuracy of auscultation for carotid bruit to identify various degrees of clinically relevant CAS based on the correct reference standard of angiography are necessary to further elucidate the true accuracy of this screening test for identifying CAS. The lack of recent publication of such studies led to my inability to identify any studies for inclusion addressing KQ2. This dearth of such studies is likely due to the fact that intra-arterial carotid angiography carries risks of micro-emboli and strokes itself, with an estimated risk for major stroke of 1% (52). Currently less invasive angiographic techniques are being employed more frequently such as magnetic resonance angiography (MRA) and computed tomography angiography with reasonable accuracy when compared to conventional angiography (53, 54). However, these tests are quite expensive, are not 100% accurate, and carry some risks for neurovascular events as well. Even more often physicians and researchers are utilizing the noninvasive tool of duplex ultrasound both to assess CAS in practice as well as a reference standard in studies of screening accuracy, as was the case in the studies discussed above for KQ2.

Still conventional angiography has 100% accuracy and remains the proper gold standard by which to judge accuracy of other CAS screening tests, especially considering the consequences of false-positives and negatives in screening protocols. Yet, because of the risks of this invasive testing, it is difficult to ethically justify subjecting asymptomatic patients with no previous history of cerebrovascular events to such a test that could lead to stroke or other poor

outcomes for the purpose of a study. Therefore most studies utilizing this reference standard have been performed in patients undergoing revascularization procedures or those who possess symptomatic CAS. Overcoming this ethical dilemma and gaining institutional review board (IRB) approval for such a study assessing accuracy of carotid bruit auscultation for detecting CAS in asymptomatic patients using the proper reference of conventional angiography will likely continue to be a difficult problem going forward. Nevertheless this type of high quality study is necessary if we wish to gain updated evidence to truly establish the accuracy of auscultation for carotid bruit as a screening test for identifying CAS.

Conclusion

The results from the studies discussed in this systematic review show with low to fair certainty that auscultation for carotid bruit has poor accuracy as a screening test in asymptomatic patients both for identifying CAS ≥ 60% as well as identifying those who will suffer a subsequent ischemic stroke. For KQ1 and KQ2, both the sensitivities and specificities were inadequate for a good screening test in the general population, with the sensitivity being especially poor concerning the test's ability to identify those who will suffer the future health outcome of stroke. Though the included studies for KQ1 did not provide accuracy measures for the outcome of TIA, the systematic review showed a risk ratio of 4.00 for this outcome in patients with bruits compared to those without. Yet just showing that those patients with carotid bruits are at increased risk of stroke and TIA compared to their counterparts without bruits does not mean that this constitutes an accurate screening test for these cerebrovascular outcomes in the population. For KQ2 the sensitivity was slightly lower and the specificity slightly higher for identifying CAS than what the USPSTF determined in their last evidence review analyzing this screening test. Yet this was based on a reference of 70-99% on angiogram compared to that of

60-99% on ultrasound, which may account for some of this difference. Nonetheless these values were relatively close and the conclusion remains the same. I can say with fair certainty that the sensitivity and specificity along with the resulting false-positive and false-negative rates of this test are too poor for it to serve as a good screening tool in the general asymptomatic population. The presence of a carotid bruit on auscultation would do a poor job identifying only those patients in the population who possess CAS $\geq$ 60% as well as those who will suffer a subsequent stroke and would benefit from treatment due to the high rate of false-positives. At the same time the absence of a carotid bruit on auscultation would poorly exclude only those patients who do not actually possess CAS $\geq$ 60% as well as those who will not suffer a subsequent stroke due to the really high rate of false-negatives.

Beyond just these accuracy measures for this specific screening test, we do not even have good evidence that applying a screening program actually reduces strokes in the population. This is in combination with the fact that we also do not know how to reliably determine which patients with clinically relevant CAS will actually suffer a stroke, providing a better pool to screen within. There have been no RCTs that directly compare a cohort of asymptomatic patients screened for carotid bruit to those not screened to assess if screening leads to less strokes and poor cerebrovascular outcomes. If we do not know with good certainty that using this screening tool will reduce cerebrovascular outcomes in our patients, then we should not utilize it in the population. This is regardless of the accuracy of the specific test as all testing and subsequent treatment presents various harms to the patient. These harms must be justified against the benefit that we get from screening. Without good understanding of the benefits from screening and what constitutes the best population to screen within, this justification cannot be well reconciled and we should not subject the general population to screening. Therefore because of inadequate

certainty of the benefit of screening for CAS in the general asymptomatic population, lack of a reliable means to delineate a more distinct group to screen in, and the poor accuracy of auscultation for carotid bruit in the primary care setting; I recommend against the use of this test to screen for CAS and future cerebrovascular outcomes as part of an overarching screening program aimed at reducing poor cerebrovascular outcomes.

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