

**Medicare Evidence Development & Coverage Advisory Committee
Management of Carotid Atherosclerosis
January 25, 2012**

The American Heart Association (AHA) and the American Stroke Association (ASA), a division of the AHA, are pleased to provide comments to the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) on the management of carotid atherosclerosis.

AHA/ASA is the nation's largest voluntary health organization with over 22.5 million volunteers and supporters. Since 1924, AHA/ASA has dedicated itself to building healthier lives free of cardiovascular disease and stroke – the #1 and #4 leading causes of death in the United States – through research, education, community-based programs, and advocacy.

AHA supports the efforts of the Centers for Medicare & Medicaid Services (CMS) and MEDCAC to determine the best treatment options for patients with carotid atherosclerosis. Carotid atherosclerosis places individuals at increased risk for a number of adverse cardiovascular events such as myocardial infarction, peripheral arterial disease, and the two outcomes of primary interest for this meeting – stroke and death. Carotid atherosclerosis or carotid stenosis is a significant risk factor for stroke. Carotid stenosis of 60% or more has been associated with approximately 7% of all first ischemic strokes.¹

Carotid atherosclerosis affects a significant portion of the Medicare population. According to data from the Framingham Heart Study, 7% of women seniors and 9% of men seniors have carotid stenosis of more than 50%. The Cardiovascular Health Study found similar results with 5% of women and 7% of men over 65 years of age with moderate carotid stenosis between 50% and 74%, and 1.1% of women and 2.3% of men with severe stenosis of more than 75%.

Because of the serious risks associated with carotid atherosclerosis, treatment of individuals at high risk for stroke, particularly among symptomatic patients, may be recommended. Treatment options include carotid endarterectomy (CEA), carotid artery stenting (CAS), or medical therapy. AHA/ASA, in conjunction with the American College of Cardiology and the American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery, has examined these various treatment options and in 2011 issued practice guidelines for the management of patients with extracranial carotid and vertebral artery disease.²

Our comments are based on these guidelines, as well as input from experts in this field, and focus on the specific topic areas the Committee has been asked to discuss today.

Risk Evaluation

Is there adequate evidence to determine if persons in the Medicare population who are asymptomatic for carotid atherosclerosis can be identified as being at high risk for stroke in either cerebral hemisphere?

There are a number of risk factors that contribute to an increased risk for stroke in patients with asymptomatic carotid atherosclerosis. Advanced age, for example, is a risk factor for stroke. The best risk factor, however, is the degree of carotid stenosis. In general, the more severe the stenosis, the greater the risk of stroke. For the asymptomatic population, a stenosis of more than 70% is considered to place the individual at increased risk for stroke. Other factors such as the characteristics of the plaque formation within the carotid artery may be useful in the identification of high risk individuals in the future, but these factors are not ready for widespread use. Outside of the severity of stenosis, we have not yet determined a mechanism to identify those at the highest risk for stroke.

In a related question, MEDCAC asks if there are ethical concerns to conducting randomized controlled trials of CEA, CAS, or best medical therapy in the general asymptomatic population, and if such trials would only be appropriate for individuals at high risk for stroke. AHA/ASA believes such trials pose no ethical issues; participants in the trials would be required to provide informed consent. In addition, well-designed, contemporary trials are needed to compare CEA, CAS, and medical therapy. Results from these trials would help the medical community determine the appropriate role of CEA, CAS, and medical therapy for asymptomatic patients. Expanding the trials to include both high and low risk patients may also be appropriate as the role of CEA, CAS, and medical therapy is a valid research question in both of these patient populations.

Is there adequate evidence to determine if persons in the Medicare population, who are considering carotid revascularization, can be identified as being at high risk for adverse events from CEA?

There are a number of co-morbidities that increase the risk of revascularization such as advanced age (> 80 years of age), New York Heart Association class III or IV heart failure, left ventricular ejection fraction < 30%, class III or IV angina pectoris, left main or multivessel coronary artery disease, the need for cardiac surgery within 30 days, a myocardial infarction within four weeks, and severe chronic lung disease. For CEA in particular, health professionals should also consider if the individual has anatomic risk factors. Unfavorable neck anatomy such as arterial stenosis distal to the second cervical vertebra or proximal (intrathoracic) arterial stenosis, previous ipsilateral CEA, contralateral vocal cord paralysis, open tracheostomy, radical surgery, and prior radiation therapy to the neck may place an individual at high risk for arterial surgery. For these patients, CAS may be a reasonable alternative to CEA when revascularization is indicated.

To identify these individuals, medical professionals should examine the individual's medical history and conduct a thorough physical exam. The individual's stroke risk, including an evaluation of cardiac function and other cerebral vessels, should also be assessed.

¹ 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease. *Circulation* 2011, 124:e54-e130.

² Ibid. See <http://circ.ahajournals.org/content/124/4/e54.full.pdf>.

Favored Treatment Strategy

For persons with symptomatic carotid atherosclerosis and carotid narrowing ($\geq 50\%$ by angiography or $\geq 70\%$ by ultrasound) who are not generally considered at high risk for adverse events for CEA, is there adequate evidence to determine whether or not either CAS or CEA is the favored treatment strategy, as compared to best medical therapy alone, to decrease stroke or death in the Medicare population?

Intervention or revascularization is the favored treatment option over best medical therapy for symptomatic patients with moderate to severe carotid stenosis who are not at high risk for CEA. Studies have shown that CEA is superior to best medical therapy in reducing the risk of stroke in these patients. While similar studies comparing CAS to best medical therapy have not been conducted, several meta-analyses of randomized trials comparing CAS to CEA found no difference in myocardial infarction, stroke, or death rates at 30 days, or in stroke or death rates at one year.³ Therefore, we can reasonably conclude that because CEA and CAS are comparable, and CEA has been shown to be superior to medical therapy, both CAS and CEA are preferable to medical therapy in this patient population.

With respect to which intervention – CEA or CAS – is most appropriate for a specific patient, the multi-society practice guidelines referenced earlier recommend the following for symptomatic patients undergoing carotid revascularization:

Class I Recommendations:

1. Patients at average or low surgical risk who experience nondisabling ischemic stroke or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax, within 6 months (symptomatic patients) should undergo CEA if the diameter of the lumen of the ipsilateral internal carotid artery is reduced more than 70% as documented by noninvasive imaging (*Level of Evidence: A*) or more than 50% as documented by catheter angiography (*Level of Evidence: B*) and the anticipated rate of perioperative stroke or mortality is less than 6%.
2. CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6%. (*Level of Evidence: B*)

Class IIa Recommendations:

1. It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular intervention. (*Level of Evidence: B*)
2. It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery. (*Level of Evidence: B*)
3. When revascularization is indicated for patients with TIA or stroke and there are no contraindications to early revascularization, intervention within 2 weeks of the index event is reasonable rather than delaying surgery. (*Level of Evidence: B*)

³ Ibid.

According to the questions posted for this meeting, MEDCAC is also interested in whether factors such as patient age, gender, and racial/ethnic background and the time to treatment affect the method of preferred method of revascularization. As noted in the Class IIa recommendation above, age is a relevant consideration. Because older patients generally have better outcomes with CEA, it is recommended that older patients undergo CEA rather than CAS. In addition, the practice guidelines also recommend that revascularization occur within two weeks of the onset of symptoms when possible.

For persons with asymptomatic carotid atherosclerosis and carotid narrowing ($\geq 60\%$ by angiography or $\geq 70\%$ by ultrasound) who are not generally considered at high risk for adverse events from CEA, is there adequate evidence to determine whether or not either CAS or CEA is the favored treatment strategy as compared to best medical therapy alone, to decrease stroke or death in the Medicare population?

The evidence comparing CEA, CAS, and best medical therapy in asymptomatic patients is lacking. Because the data are not as strong and asymptomatic patients are at lower risk for stroke, more conservative treatments are generally recommended.

For asymptomatic patients, the practice guidelines recommend:

Class IIa:

1. It is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low. (*Level of Evidence: A*)

Class IIb:

1. Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established. (*Level of Evidence: B*)

Because the data comparing CEA, CAS, and best medical therapy in asymptomatic patients are not as robust as we would like – particularly for the use of CAS in asymptomatic patients – we would like to see additional data from randomized controlled trials that compare the three therapies. This is an area that warrants further research.

For persons with asymptomatic carotid atherosclerosis who are not generally considered at high risk for stroke in either cerebral hemisphere, is there adequate evidence to determine whether or not CAS or CEA or best medical therapy alone is the favored treatment strategy to decrease stroke or death in the Medicare population?

This question focuses on asymptomatic patients who are not at high risk for stroke. If, as with the first question, we use the degree of stenosis as the marker for stroke risk, this question applies to asymptomatic patients who have less than 70% stenosis.

In this patient population, there is no evidence that demonstrates that revascularization – either CEA or CAS – is better than best medical therapy.

In response to the Advisory Committee's follow-up question regarding the use of best medical therapy concurrently with CAS or CEA, we believe that all patients should receive best medical therapy either as a stand-alone treatment or in conjunction with revascularization.

Screening for Carotid Atherosclerosis

In the general Medicare population, is there adequate evidence to determine whether or not carotid artery screening of asymptomatic persons decreases stroke or death?

Available evidence does not support the use of carotid artery screening of asymptomatic persons as a means to decrease stroke or death. In general, carotid artery screening of asymptomatic patients is not recommended. The practice guidelines consider carotid artery screening of most asymptomatic individuals to have no benefit.

Class III Recommendations: No Benefit:

1. Carotid duplex ultrasonography is not recommended for routine screening of asymptomatic patients who have no clinical manifestations of or risk factors for atherosclerosis. *(Level of Evidence: C)*
2. Carotid duplex ultrasonography is not recommended for routine evaluation of patients with neurological or psychiatric disorders unrelated to focal cerebral ischemia, such as brain tumors, familial or degenerative cerebral or motor neuron disorders, infectious and inflammatory conditions affecting the brain, psychiatric disorders, or epilepsy. *(Level of Evidence: C)*
3. Routine serial imaging of the extracranial carotid arteries is not recommended for patients who have no risk factors for development of atherosclerotic carotid disease and no disease evident on initial vascular testing. *(Level of Evidence: C)*

The guidelines, however, include a few exceptions for asymptomatic individuals who either exhibit some sign such as a carotid bruit that may be indicative of carotid stenosis or who have a number of risk factors. However, as noted below, it is still unclear if carotid artery screening of these patients, which results in a diagnosis of carotid atherosclerosis, will ultimately affect the clinical outcomes.

Class IIa Recommendation:

1. It is reasonable to perform duplex ultrasonography to detect hemodynamically significant carotid stenosis in asymptomatic patients with carotid bruit. *(Level of Evidence: C)*

Class IIb Recommendations:

1. Duplex ultrasonography to detect hemodynamically significant carotid stenosis may be considered in asymptomatic patients with symptomatic PAD, coronary artery disease (CAD), or atherosclerotic aortic aneurysm, but because such patients already have an indication for medical therapy to prevent ischemic symptoms, it is unclear whether establishing the additional diagnosis of ECVD in those without carotid bruit would justify actions that affect clinical outcomes. *(Level of Evidence: C)*
2. Duplex ultrasonography might be considered to detect carotid stenosis in asymptomatic patients without clinical evidence of atherosclerosis who have 2 or more of the following risk factors: hypertension, hyperlipidemia, tobacco smoking, a family history in a first degree relative of atherosclerosis manifested before age 60 years, or a family history of

ischemic stroke. However, it is unclear whether establishing a diagnosis of ECVD would justify actions that affect clinical outcomes. (*Level of Evidence: C*)

Future Research

What unmet research needs, specific to the following issues are important to consider and explore further?

Should future stroke prevention trials:

- *Be powered to evaluate only symptomatic or asymptomatic patients?*
- *Be powered to draw conclusions regarding gender?*
- *Evaluate outcomes for more racially/ethnically diverse patient populations?*

We would like to see future research that examines stroke prevention in both symptomatic and asymptomatic patients. However, because we have less information on stroke prevention in asymptomatic patients, it is particularly important that future research focus on the asymptomatic patient population.

We would also like future research to examine the impact of gender and race/ethnicity. We are aware, however, that it is unlikely that one study will have sufficient power to evaluate all of these factors. In addition, it may be difficult for studies to evaluate certain factors such as clinical outcomes specific to females since women generally have lower event rates.

So as to help delineate those who require carotid revascularization from those who do not, how should future trials best utilize and validate for the Medicare population the following tools to identify persons with asymptomatic carotid atherosclerosis who are at high risk for stroke?

- *Advanced imaging, such as 3D ultrasound, for plaque morphology*
- *Transcranial Doppler (TCD) for cerebral microembolization*
- *Pre- and post-procedure diffusion weighted MRI (DW-MRI) for silent infarcts*
- *Risk assessment tools and predictive stroke models*

All of the tools listed above could be of some use in identifying asymptomatic patients who are at high risk for stroke. However, each technique would have to first be validated for its ability to reliably predict risk. We therefore recommend that these tools be incorporated into future clinical trials and evaluated to determine which mechanism(s) are appropriate for stroke risk stratification.

Conclusion

In closing, thank you again for the opportunity to provide the American Heart Association's and the American Stroke Association's views on the management of carotid atherosclerosis. Carotid atherosclerosis is an important health issue for the Medicare program, affecting approximately 10% of all Medicare beneficiaries and placing them at increased risk of stroke – the number four killer of all Americans. To ensure that Medicare beneficiaries with carotid atherosclerosis receive appropriate diagnosis and treatment, we encourage CMS to implement the recommendations contained in the 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease.