Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 49

Effectiveness and Cost-Effectiveness of Echocardiography and Carotid Imaging in the Management of Stroke

Summary

Overview

Each year, 600,000 Americans have strokes: of these, 500,000 are first attacks. In 1997, stroke directly accounted for about one of every 14.5 deaths (160,000 total) in the United States. Stroke was the third leading cause of death behind non-stroke-related heart disease and cancer, and was an underlying or contributing cause of 280,000 deaths. There are currently 4.4 million stroke survivors in the U.S., many of whom experience serious, long-term disability; 15 to 30 percent of stroke survivors are permanently disabled.

The economic costs of stroke are also substantial—$51.3 billion in 1999, about 16 percent of the total economic burden of all cardiovascular diseases. This includes $30.6 billion in direct health expenditures and $21.7 billion in lost productivity from morbidity and mortality. This estimate excludes the losses of quality of life experienced by the stroke patient and his or her family.

About 85 percent, or 510,000, of all strokes in a given year (including most recurrent strokes) are ischemic in nature. Identification of a particular stroke mechanism guides clinical decisionmaking about therapy. The purpose of imaging procedures such as transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and carotid ultrasound (CUS) is to detect cardiac and carotid sources of cerebral emboli. However, the most effective and cost-effective policies for implementing these technologies and the patient subgroups for which they provide greatest benefit are unclear. Although a 1997 cost-effectiveness analysis concluded that TEE should be performed on all new-onset stroke patients, other studies have not supported this strategy. Cardiogenic embolism accounts for 15 to 30 percent of ischemic strokes, which suggests that a broad range of patients with stroke (50,000 to 150,000) may be candidates for echocardiography in the U.S. annually. Yet, many patients with cardiogenic emboli also have other conditions, such as atrial fibrillation (AF), that warrant anticoagulant therapy, obviating the need for echocardiography in therapeutic decisionmaking. In addition, for many cardiac lesions that are potentially identifiable by echocardiography, both the rate of recurrent stroke associated with these lesions and the effectiveness of therapy in lowering the recurrent stroke rate are largely unknown. Because of the cost of these procedures, as well as the discomfort and potential risk associated with TEE, the appropriate choice of echocardiographic procedure (TTE, TEE, or a combination), and their use within particular patient subgroups, are important issues.

Similar questions arise regarding the use of carotid imaging procedures to determine patient subgroups most likely to benefit from carotid endarterectomy (CEA). Although cerebral angiography is considered the gold standard for determining the level of carotid stenosis, it is an expensive, invasive test that is not risk-free. Some physicians have advocated greater use of non-invasive procedures such as CUS and magnetic resonance angiography (MRA). Although MRA is more expensive than CUS ($900 to $1,200 versus $200 to $250), both procedures are less expensive but also less accurate than cerebral angiography ($2,000 to $2,500). This introduces the possibility of inappropriate surgery when noninvasive tests are used alone to select patients for CEA, which carries a relatively small risk of death, but a higher and more variable risk of perioperative stroke.

This evidence report analyzes the available data on the effectiveness and cost-effectiveness of imaging strategies in the evaluation and management of new stroke patients. Investigators at the Oregon Health & Science University and the Kaiser Permanente Center for Health Research, both in Portland, Oregon, collaborated on this report.

Reporting the Evidence

This report addresses key questions in two areas:

Echocardiography

1. Which clinically inapparent abnormalities identified by echocardiography among patients presenting with a new ischemic brain syndrome represent risk factors for recurrent stroke?
2. What is the yield of echocardiography in detecting potential sources of cardioembolism among patients with a new ischemic brain syndrome?
3. What are the operating characteristics (sensitivities, specificities, and likelihood ratios) of transthoracic and transesophageal echocardiography in detecting potential sources of cardioembolic stroke?
4. What are the incidence and nature of complications associated with transesophageal echocardiography?
5. Are there clinically identifiable groups of patients with new ischemic brain syndrome who benefit from anticoagulation?
6. Are there echocardiographically identifiable groups of patients with new ischemic brain syndrome who benefit from anticoagulation?

Carotid Imaging

1. What are the operating characteristics of available tests for measuring carotid artery stenosis?
2. What is the incidence of complications associated with cerebral angiography?
3. What is the efficacy of carotid endarterectomy in reducing the rate of recurrent stroke among symptomatic patients with carotid artery stenosis?
4. What is the incidence of complications associated with carotid endarterectomy?
5. Does timing affect the safety of carotid endarterectomy?

Cost Effectiveness

The overarching question for the cost-effectiveness analyses of both echocardiography and carotid imaging in patients with stroke is: what is the cost-effectiveness of routine vs. selective imaging procedures in patients with a new ischemic stroke or transient ischemic attack (TIA)? The following is a list of subquestions:

1. Of routine, selective, and no imaging, what is the most cost-effective strategy to reduce the risk of recurrent stroke associated with modifiable risk factors potentially identifiable by imaging?
2. How do cost-effectiveness estimates change with differences in clinical and demographic factors?
3. How do cost-effectiveness estimates change with differences in treatment effectiveness?
4. How do cost-effectiveness estimates change with differences in other uncertain model parameters?

Methodology

A technical expert advisory group helped refine the key questions. The group included two neurologists, a vascular surgeon, a cardiologist, a primary care clinician who is medical director of a managed care plan, and a patient who had recently had a stroke.

MEDLINE®, HealthSTAR, the Cochrane Controlled Trials Register, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness, and Health Technology Assessment from 1966 or their inception were searched. Searches were limited to human and the English language, and editorials and case reports were excluded. Three searches were related to echocardiography. A search on echocardiography and stroke identified studies relevant to echocardiography questions 1, 2, and 3. A search on transesophageal echocardiography complications identified studies relevant to question 4. For questions 5 and 6, a series of six small searches were related to anticoagulation therapy and stroke. Three searches identified studies relevant to the carotid imaging key questions. A search on carotid imaging found studies for question 1. A search on cerebral angiography complications identified studies relevant to question 2, and a search on carotid endarterectomy complications found studies relevant to questions 4 and 5. For question 3 on CEA efficacy, existing systematic reviews were used.

In addition, searches focused on the economic aspects of echocardiography and stroke, anticoagulation, carotid imaging, and carotid endarterectomy. Three databases, MEDLINE®, HealthSTAR, and the NHS Economic Evaluation Database, were searched to find papers related to costs and cost analysis, quality of life, and life expectancy and mortality to use in conducting the cost analyses.

For each key question, two investigators independently reviewed the titles and abstracts retrieved by the database searches, using predetermined inclusion/exclusion criteria, and

then compared results. Differences were resolved by a discussion between the two reviewers for that question.

For all key questions excluding those related to echocardiographic yield, complications of testing and treatment, and cost analyses, the quality criteria developed by the current U.S. Preventive Services Task Force (USPSTF) were used. In this rating system, the internal validity and applicability (external validity) of each study is rated as good, fair, or poor, based on specific criteria for that type of study design. Then the overall evidence about the question is rated as good, fair, or poor.

The USPSTF criteria for case-control and cohort studies was modified to assess internal validity of articles reporting the diagnostic yield of echocardiography and those reporting complication rates for carotid endarterectomy, cerebral angiography, and transesophageal echocardiography. Supplemental analyses were performed to determine the relative influence of each of the quality ratings criteria and the overall quality score on reported complication rates.

Two separate semi-Markov decision models analyzed the cost-effectiveness of (1) echocardiographic strategies in the evaluation of patients with stroke or transient ischemic attack to identify a potential cardioembolic source of stroke, and (2) carotid imaging strategies in the evaluation of such patients to identify a potential carotid source of stroke. A Markov model is a state-transition model in which persons entering the model cycle within and between different health states according to specified probabilities. Markov models in decision analyses related to health care interventions are typically used to simulate the natural history of a disease or condition. The prognosis of the patient (or cohort) in the analysis is described by the health states, the permissible transitions between states, and the rates of transition. Markov models can illustrate the relationship between the risk reduction of an intervention and the cost of a diagnostic or treatment strategy over the appropriate time horizon. In a pure Markov model, transition probabilities are fixed over time. Semi-Markov models for this report use a generalization of Markov processes in which transition rates between states are not fixed, but rather, can change with time (e.g., the probability of death in our model increases over time, as subjects in the model became older).

Testing procedures in the echocardiography model were TTE and TEE; in the carotid imaging model, they were CUS, MRA, and cerebral angiography. Treatment options in the echocardiography model were anticoagulation or standard medical treatment; in the carotid imaging model, they were carotid endarterectomy or standard medical treatment. Both models followed a hypothetical cohort of stroke patients over time to simulate the time sequence of health states, survival, and associated costs. This process was repeated for each study arm, which represented a different diagnostic testing strategy, not a different treatment once diagnosed. Sensitivity analyses were performed on various model parameters.

Findings

Echocardiography

The effectiveness of echocardiography as a tool in the evaluation of patients with cerebral ischemia or infarction has not been established directly. Specifically, there have been no clinical trials comparing outcomes among patients managed with and without echocardiography after stroke or TIA. Assessing the usefulness of echocardiography in such patients therefore involves examining the evidence for several assertions that serve as links in a causal pathway between echocardiography and clinical outcomes, particularly recurrent stroke. These assertions are as follows:

- Clinically inapparent abnormalities identified by echocardiography convey increased risk of recurrent stroke.
- The prevalence of these abnormalities is not inconsequential.
- Echocardiography is accurate in diagnosing these abnormalities.
- Adverse events associated with echocardiography are small or infrequent compared to its benefits.
- Efficacious treatments exist that reduce morbidity and mortality associated with potential sources of cardioembolic stroke identified by echocardiography.
- Adverse events associated with these treatments are small or infrequent compared to their benefits.

Key Question 1. Which clinically inapparent abnormalities identified by echocardiography among patients presenting with new ischemic brain syndrome represent risk factors for recurrent stroke?

Approximately 15 percent of strokes are thought to be attributable to cardioembolic sources. Some of the processes that give rise to cardioembolic stroke, most notably atrial fibrillation, are usually clinically apparent at the time a patient presents with a stroke. Other conditions, however, are clinically occult but may be identifiable with the use of imaging procedures such as echocardiography. The usefulness of echocardiography in the management of stroke depends on the ability to identify cardiac lesions and on the presence and modifiability of recurrent stroke risk conveyed by those lesions.

Several different cardiac and aortic abnormalities identifiable by echocardiography have been studied as potential sources of cardioembolic stroke. There is fair overall evidence that left

ventricular thrombus (LVT) is associated with an increased risk of systemic embolization, including stroke. Evidence regarding the presence and degree of stroke risk associated with left atrial thrombus (LAT) is insufficient to draw firm conclusions. There is fair evidence that complex aortic atheromas (ulcerated, mobile, or > 4 mm in thickness) represent risk factors for stroke, independent of coexisting carotid artery disease. There is also fair evidence for an association between atrial septal aneurysm (ASA) and stroke, particularly in the presence of coexisting patent foramen ovale (PFO). PFO alone may be an important risk factor for stroke in young patients, but evidence for an association is conflicting. Epidemiological studies of left atrial myxoma and stroke are lacking, but several case series suggest a substantially higher prevalence of stroke in patients with myxoma than in the general population. Evidence for an independent association of left ventricular aneurysm, spontaneous echocardiographic contrast, and valvular strands with stroke is insufficient. Previously documented associations between mitral valve prolapse (MVP) and stroke were likely due to inaccuracy in the determination of MVP with early echocardiographic techniques. Finally, mitral annular calcification appears to be an indicator of atherosclerotic vascular disease rather than an independent cause of stroke.

It must be emphasized that the absence of sufficient evidence regarding an association between a cardiac abnormality and stroke does not necessarily indicate that an association does not exist. When biomedical knowledge and experience suggest a high likelihood that a particular lesion, such as intracardiac thrombus, is an independent risk factor for stroke, that likelihood remains high in the face of inconclusive evidence.

Key Question 2. What is the yield of echocardiography in detecting potential sources of cardioembolism among patients with a new ischemic brain syndrome?

The review of echocardiographic yield focused primarily on intracardiac thrombi, ASA, complex aortic atheroma, and atrial myxoma (lesions for which there was fair to good evidence of an independent association with stroke). Researchers analyzed the prevalence of these lesions as detected by TTE and TEE, in unselected patients, patients with and without cardiac disease, patients without significant carotid artery stenosis, and young patients (under 50) with stroke. The yield of intracardiac thrombi using TTE was highly variable. In one study of good quality from Japan, the prevalence of intracardiac thrombus in consecutive patients with stroke or TIA undergoing TTE was 2.1 percent (95 percent confidence interval [CI], 0.8 to 4.6 percent). In three fair-quality studies, no cases of thrombus were diagnosed in patients without heart disease. Among patients with heart disease, the prevalence of thrombus was highly variable, ranging from 0 to 36 percent. This variability, as well as small sample sizes, made it difficult to derive a reliable estimate of the yield of TTE among patients with a history of cardiac disease or without significant carotid disease. One atrial myxoma was diagnosed among 721 patients in eight studies. In most studies, LAT, ASA, and aortic atheroma were not found using TTE in patients without AF.

In two studies of TTE among young patients (aged 15 to 45) with stroke, the pooled prevalence of intracardiac thrombus in 180 patients was 2.2 percent (similar to that in unselected patients). No left atrial myxomas were detected. The prevalence of any unsuspected thrombus, tumor, valvular vegetation, or cardiomyopathy was 4.4 percent (95 percent CI, 2.1 to 8.2).

The overall yield of intracardiac thrombus using TEE in consecutive stroke patients was 1.7 percent (95 percent CI, 0.5 to 5.3 percent). The prevalence of heart disease was not reported in most studies of TEE, making it difficult to determine the importance of this variable. In four studies of patients without significant carotid disease, the prevalence of intracardiac thrombus on TEE was highly variable, ranging from 1.5 to 18 percent. One myxoma was detected among approximately 1,200 patients examined. The yield of ASA (3.8 to 21.6 percent) and complex aortic atheroma (1.9 to 17.2 percent) using TEE varied widely across studies. One study of patients under 60 with negative TTE reported a prevalence of ASA of 28 percent, with 15 percent having both ASA and PFO. The prevalence of complex aortic atheroma in this study excluding elderly patients was 3.4 percent.

The finding from previous reviews of a higher yield of intracardiac thrombus and other potential sources of stroke using TEE largely reflects the inclusion in those reviews of patients with AF. Findings in the current review suggest that in patients without AF, TEE may be less useful than previously described. TEE may have advantages in patients who have insignificant or no carotid disease or who have a negative TTE. There is little information on the yield of TEE in patients with pre-existing heart disease other than AF.

Key Question 3. What are the operating characteristics (sensitivities, specificities, and likelihood ratios) of transthoracic and transesophageal echocardiography in detecting potential sources of cardioembolic stroke?

Because of the relatively low prevalence of intracardiac thrombus in patients with stroke, it is difficult to assess the accuracy of TTE and TEE in this population. Studies attempting to determine the accuracy of these tests for LAT and LVT, as detected by direct intracardiac inspection, have necessarily examined populations in which the prevalence of thrombus is high. These populations, patients undergoing

surgery for severe mitral valve disease or left ventricular aneurysms, are not representative of the general population of patients with stroke, and thrombi occurring in these patients may differ substantially from those likely to affect patients with cardioembolic stroke. It is therefore possible that the reported accuracy estimates in these studies differ from the accuracy of TTE and TEE in patients with stroke.

The average sensitivity and specificity of TEE in detecting LAT in these studies were 93 and 97 percent, respectively. For TTE, sensitivity and specificity averaged 42 and 99 percent. The low sensitivity of TTE was largely due to missed left atrial appendage thrombi. For the diagnosis of LVT, TTE had an average sensitivity of 78 percent and specificity of 87 percent. When results from individual studies were plotted on a summary receiver operating characteristic (SROC) curve, however, it appeared that varying accuracy across studies may have been partly due to differing diagnostic thresholds. Using the SROC curve to estimate the accuracy, the sensitivity and specificity of TTE for diagnosing LVT were 77 and 95 percent, respectively. It should be noted, however, that approximately 15 percent of TTE examinations in studies of LVT were deemed inadequate for interpretation, limiting the diagnostic utility of this test. No studies of the accuracy of TEE in diagnosing LVT were identified.

When the prevalence of intracardiac thrombi in patients with stroke is assumed to be 2 percent or less, as many as or more patients will receive unnecessary treatment due to false positive tests than will receive potentially beneficial treatment for a true positive test, if echocardiographic technology is used to select patients for treatment with anticoagulants. Under current estimates of test accuracy, the prevalence of LAT would have to exceed 15 percent and the prevalence of LVT 37 percent in order to achieve 90 percent predictive value.

Studies examining the accuracy of echocardiography in diagnosing ASA and aortic atheroma are lacking. However, given that the association with stroke has been established for the echocardiographic, rather than anatomic, definitions of these lesions, it may be argued that TEE represents the gold standard for the diagnosis of these lesions as they relate to cardioembolic stroke. Few studies have assessed the accuracy of echocardiography in diagnosing left atrial myxoma. These studies suggest accuracy approaching 100 percent, though one study found disagreement between TTE and TEE in 2 of 11 cases.

Key Question 4. What are the incidence and nature of complications associated with transesophageal echocardiography?

In observational studies of poor and fair quality, the pooled risk of periprocedural death associated with TEE was 0.014 percent. The risk of death in patients specifically undergoing TEE for evaluation of possible cardiac embolus could not be directly calculated. Data were insufficient to determine whether the risk of death was higher in elderly or critically ill patients.

From observational studies of fair quality, the average risk of major (requiring treatment) cardiovascular, pulmonary, and gastrointestinal complications from TEE was 0.7 percent. The rates of major complications in elderly and critically ill patients were 0.4 percent and 0.8 percent, respectively. Neither of these rates was significantly different from the overall rates. No cases of infective endocarditis or systemic infection were found in 775 patients followed after TEE. Approximately 1.9 percent of TEE were unsuccessfully attempted, and an additional 0.9 percent were stopped for complications, most frequently patient intolerance. The rate of minor complications (most commonly patient intolerance) requiring discontinuation of the procedure was not consistently reported, but appears to be about three times the rate of major complications.

Although the estimates of risk came from studies of poor or fair methodological quality (no included study was assessed as having overall good quality), no other data were available to provide more reliable estimates. Data are insufficient to determine whether complication rates are different in patients presenting with particular indications such as cerebral ischemic syndromes.

Key Question 5. What is the efficacy of anticoagulant therapy in reducing the rate of recurrent stroke among patients with potential sources of cardioembolism?

For any given patient with stroke, the potential usefulness of echocardiography in detecting a source of cardioembolism depends on the absence of clinically apparent indications for treatment (i.e., anticoagulation). There is substantial evidence, for instance, that for patients with stroke and AF, anticoagulant drugs confer net benefit, making echocardiographic identification of lesions warranting anticoagulation in these patients superfluous. Whether anticoagulation is beneficial in stroke patients without AF is less clear.

There is fair evidence that unselected patients with stroke do not benefit from anticoagulation as compared to antiplatelet therapy. Evidence from a large, fair-quality international trial suggests that subcutaneous heparin given acutely to patients with stroke is not associated with improved outcomes when compared to aspirin. The two therapies used in combination may confer net benefit, but further study is needed to confirm this finding. A good-quality multicenter trial comparing chronic anticoagulation (target INR 1.4–2.8) and aspirin (325 mg) found no differences in either benefits or harms between the two treatments. Another good-quality trial employing higher degrees of anticoagulation (target INR

3.0–4.5) was stopped early due to increased rates of ICH and death with anticoagulation as compared to aspirin.

No fair- or good-quality studies were found examining the effectiveness of anticoagulation in the prevention of recurrent stroke among patients with stroke and cardiac conditions other than AF. Studies of primary stroke prevention among patients with MI (myocardial infarction) suggest that when compared to aspirin, anticoagulation either alone or in combination with aspirin does not confer net benefit. For patients with dilated cardiomyopathy (DCM), evidence regarding anticoagulation for primary stroke prevention comes from observational studies that provide conflicting results. The only good-quality study found that anticoagulation was more effective than aspirin in the primary prevention of stroke, particularly for patients with moderate and severe cardiomyopathy, after acute MI.

Overall, there was fair evidence that neither acute nor chronic anticoagulation confers net benefit, as compared to aspirin, for unselected patients with stroke. Also, there was insufficient evidence to reach conclusions regarding the effectiveness of anticoagulation for secondary prevention of stroke among patients with stroke and clinically apparent cardiac conditions other than AF. Studies of primary prevention suggest that anticoagulation may be beneficial for patients with DCM but is probably not beneficial in patients with MI; however, results from studies of primary stroke prevention may not be generalizable to patients who have already experienced stroke and are candidates for secondary prevention. Given these findings, it appears that the scope of patients for whom echocardiography may be useful, if it can effectively identify treatable sources of recurrent stroke, includes all stroke patients except those with AF.

Key Question 6. Are there echocardiographically identifiable groups of patients with new ischemic brain syndrome who benefit from anticoagulation?

Studies of the effectiveness of anticoagulation for echocardiographically identifiable lesions were all observational in design. Pooled data from five retrospective cohort studies suggest that warfarin, and possibly surgical PFO closure, may reduce the rate of recurrent stroke or TIA among patients with stroke and PFO. However, these studies were generally of poor quality and did not account for differences in baseline characteristics that may have given rise to differences in outcomes across treatment groups. A small, poor–quality cohort study of patients with stroke found to have mobile aortic atheromas revealed a trend toward lower recurrent stroke rates with warfarin as compared to aspirin, but no death. A poor-quality systematic review of primary stroke prevention in patients with intraventricular thrombus after acute MI suggested a net benefit with anticoagulation, but the reviewed studies were observational, and no adjustment for potential confounding was conducted. Moreover, whether or not findings from studies of primary stroke prevention among patients with acute MI can be used to draw conclusions regarding secondary prevention among a general population of patients with stroke is not clear. Researchers found insufficient evidence to draw conclusions about the effectiveness of anticoagulation in reducing morbidity and mortality among stroke patients with echocardiographically identified lesions.

Cost-Effectiveness

Because of the lack of solid evidence for important components of effectiveness, it is difficult to accurately estimate the cost-effectiveness of echocardiography in the management of stroke. Where evidence was lacking or insufficient, informed assumptions were made to enable estimating cost-effectiveness. Assumptions include the following: intracardiac thrombus conveys increased stroke risk for the first year after the initial stroke; thrombus prevalence is 2 percent in unselected patients and 5 percent in patients with heart disease; and anticoagulant drugs reduce the risk of recurrent stroke by one-third. Using those assumptions, one quality-adjusted life year (QALY) can be saved for an approximate incremental cost of $300,000, using TEE only in patients with heart disease. Other strategies were less cost-effective, though TTE in patients with heart disease was the preferred strategy under some plausible assumptions. The cost-effectiveness ratio for either echocardiographic procedure fell below $50,000 per QALY if the assumed relative risk reduction with anticoagulation was increased to 86 percent and the prevalence of thrombus was simultaneously increased to 6 percent. The cost per QALY of all strategies increased as average life expectancy diminished (e.g., with increasing age or comorbidity).

Carotid Imaging

The role of carotid imaging is better established than that of echocardiography in patients with stroke. It is clear that carotid artery stenosis conveys increased risk of stroke and that efficacious treatment exists to reduce that risk. However, the most effective imaging strategy for diagnosing carotid artery stenosis is controversial. The most widely used tests include two noninvasive tests, carotid ultrasound and magnetic resonance angiography, and one invasive test, cerebral angiography. These tests may be used alone or in various combinations. Although the noninvasive tests are not associated with significant complications, their effectiveness in predicting who will benefit from surgical intervention has not been directly established, as it has for angiography. The noninvasive tests therefore carry the potential for false positive and false negative diagnoses and the consequent risk of selecting patients without significant carotid stenosis for ineffective and potentially harmful surgery, or excluding

patients with significant stenosis from beneficial treatment. In order to compare the effectiveness of various strategies for carotid imaging, evidence related to the following was examined:

- Operating characteristics (sensitivities, specificities, and likelihood ratios) of available tests for measuring carotid stenosis.
- Harms associated with these tests.
- Efficacy of treatment for varying degrees of carotid stenosis.
- Harms associated with these treatments.

Key Question 1. What are the operating characteristics of available tests for measuring carotid artery stenosis?

Despite numerous studies of the accuracy of noninvasive carotid imaging, relatively few have been conducted in which all patients undergoing noninvasive tests also undergo diagnostic confirmation with cerebral angiography. The lack of diagnostic verification in these studies creates biased estimates of sensitivity and specificity. Studies can adjust for this bias by angiographically studying a random sample of subjects with negative noninvasive tests. Studies were reviewed of CUS and MRA accuracy that either had no obvious or likely verification bias or that adjusted for this bias.

It is clear from the literature that the accuracy of CUS in diagnosing carotid stenosis varies substantially across centers. It is likely that published reports of the accuracy of CUS from single centers overestimate the accuracy in most settings. This has two important implications. First, it may be inappropriate for individual practitioners or medical centers to assume that the accuracy of CUS in their practices is equivalent to published figures. Second, it is clear that there is potential for CUS to be highly accurate. The sensitivity and specificity of CUS estimated from SROC curves constructed from the results of eight predominantly fair-quality studies were 80 and 91 percent, respectively, for moderate or greater (> 50 percent) stenosis, and 75 and 87 percent for severe (> 70 percent) stenosis. When the largest and only good-quality study was excluded, sensitivity and specificity for severe stenosis rose to 94 and 84 percent. The lower accuracy in the largest study than in other studies may have been due to the use of conventional rather than color-flow duplex imaging, but may also have been due to the representation of multiple centers. Reports from single centers may provide biased estimates of accuracy, as those centers finding low accuracy may choose not to submit their results for publication.

Whether the accuracy of MRA varies by center is not clear. There have not been multicenter studies of MRA. Published data, excluding studies with obvious or likely verification bias, suggest a sensitivity and specificity of 92 and 97 percent for detecting severe stenosis. However, studies of MRA were generally of fair to poor quality. As with CUS, it is possible that centers publishing their accuracy data are not representative of all users of MRA. Until there are more high-quality data on the accuracy of MRA, current estimates of MRA accuracy in measuring carotid stenosis must be interpreted cautiously.

All studies of the accuracy of CUS and MRA used in combination were biased by incomplete verification. In the majority of these studies, sensitivity was 100 percent. However, the studies were generally of poor quality. The specificity of combined CUS and MRA was variable, ranging from 69 to 100 percent. The estimated sensitivity and specificity of combined CUS and MRA for detecting severe stenosis were 95 and 98 percent, respectively. In approximately 18 percent of patients, the results of CUS and MRA in detecting severe stenosis were discordant.

Key Question 2. What is the incidence of complications associated with cerebral angiography?

In prospective studies examining the incidence of stroke and death following cerebral angiography in patients suspected of having cerebrovascular disease and potential candidates for CEA, the overall rate of 0.02 percent for deaths was lower than the 0.08 percent rate previously reported. Only two deaths were found in 10 studies including 3,074 patients.

Significant heterogeneity was found between rates of combined stroke or death from all studies as well as between studies stratified by various methodologic criteria. The rate of combined stroke or death ranged from 0 percent to 4 percent in three studies rated as having good quality, with the study rated as having the highest quality reporting a rate of 1.3 percent (95 percent CI, 0.5 to 2.8 percent).

The risk of complications appears higher in patients with greater degrees of carotid stenosis, who are also those patients most likely to benefit from subsequent CEA.

The magnitude of incremental risk of cerebral angiography (i.e., the risk above the baseline risk of recurrent stroke or death in recently symptomatic patients) cannot be reliably estimated at this time but would be expected to be lower than the rates reported above.

Key Question 3. What is the efficacy of carotid endarterectomy in reducing the rate of recurrent stroke among symptomatic patients with carotid artery stenosis?

In two large, good-quality randomized controlled trials (RCTs), carotid endarterectomy reduced the risk of disabling stroke or death for surgically fit patients with symptomatic ipsilateral stenosis greater than 70 percent as measured by the European Carotid Surgery Trial (ECST) method, and over 50 percent as measured by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. In a meta-analysis of these trials, the number needed to treat to prevent

one disabling stroke or death over 2 to 6 years was 15 (95 percent CI, 10 to 31) for severe stenosis (70 to 99 percent by NASCET criteria or 80 to 99 percent by ECST criteria) and 21 (95 percent CI, 11 to 125) for moderate stenosis (50 to 69 percent by NASCET or 70 to 79 percent by ECST). No benefit was seen in patients with lesser degrees of carotid stenosis. In the subgroup of patients with severe stenosis, increased degree of stenosis was associated with greater benefit from surgery. The results of the studies are generalizable to surgeons and centers with low perioperative complication rates (30-day stroke or death rate less than 6 percent). The studies did not include angiographic morbidity or mortality in their results.

Although patients over 80 years old, non-whites, and females were underrepresented in these studies, multivariate analysis to determine factors associated with increased benefit was performed on these and other clinical and demographic characteristics in the two trials. In NASCET and ECST, less benefit was seen in females for all degrees of carotid stenosis, and among patients with 50 to 69 percent stenosis, the absolute risk reduction was eight-fold lower in women than in men. The lesser degree of benefit for women may be partially due to a lower baseline recurrent stroke rate compared to men for equivalent degrees of carotid stenosis. Older age was associated with increased benefit in ECST and in the subgroup of patients in NASCET with 70 to 99 percent stenosis.

It must be noted that among patients screened in the NASCET, fewer than one-third were randomized. Approximately one-third did not fulfill baseline criteria, 15 percent were excluded for medical reasons, and another 23 percent were eligible but not randomized. Such exclusions must be considered when trying to generalize data from the endarterectomy trials to individual patients or populations of patients in "real-world" health care settings.

Key Question 4. What is the incidence of complications associated with carotid endarterectomy?

Using data from 12 studies of good quality, the pooled rate of combined perioperative (30-day) stroke or death associated with CEA was 6.8 percent (95 percent CI, 4.6 to 9.5 percent), and from nine studies of good quality, the pooled rate of death alone was 1.6 percent (95 percent confidence interval, 1.0 to 2.5 percent).

In NASCET, the 30-day postrandomization rate of stroke or death ranged from 2.4 percent (for patients with < 70 percent carotid stenosis) to 3.3 percent (70 to 99 percent stenosis) in patients assigned to medical therapy. Therefore, surgery is associated with an additional 35 to 44 perioperative events per 1,000 patients. In NASCET, approximately 60 percent of the strokes that occurred in the perioperative period were nondisabling (Rankin score < 3).

Methodologic characteristics of the studies explained some of the variation in complication rates. Population-based studies, RCTs, studies with independent ascertainment of complications, studies with nonsurgeon authors, and studies published since 1990 were associated with higher combined complication rates. The pooled complication rate in randomized controlled trials was higher than the pooled rate for other studies, suggesting that these trials may have high generalizability despite strict selection criteria. Population-based studies also reported relatively high perioperative complication rates. All of the characteristics associated with higher complication rates appear to occur in studies rated as having higher average methodologic quality.

Key Question 5. Does timing affect the safety of carotid endarterectomy?

The appropriate timing of carotid imaging depends partly on the timing of CEA. CEA is often delayed for several weeks after stroke onset due to concerns about the safety of CEA in the acute period. There is fair evidence that early as compared with delayed CEA is not associated with an increased risk of major complications. Three nonrandomized studies of fair quality suggest that in patients with recent minor or nondisabling stroke, CEA performed earlier than the traditional waiting period of 4 to 6 weeks is not associated with significantly increased adverse events compared to delayed surgery, with a pooled rate of 3.3 percent for early CEA versus 5.3 percent for later CEA. When data from all studies (including seven rated poor quality) are included, the pooled rate of major perioperative complications (stroke or death) is 3.9 percent for early CEA versus 2.7 percent for later CEA. The pooled rate of death alone from all studies was about 1.0 percent in patients undergoing either early or later CEA. There was a nonsignificant trend toward better outcomes for early CEA in studies published since 1990.

There is insufficient evidence to draw conclusions regarding the risk of very early CEA (i.e., less than 1 week after presenting with symptoms). There is also inadequate evidence to draw conclusions for specific subgroups, including patients with specific computed tomography scan findings and greater degrees of carotid stenosis. Patients selected for early CEA in these studies are likely to comprise an overall lower-risk population compared to patients not selected for early CEA, though in higher-quality studies patients undergoing early and later CEA were comparable according to important clinical and demographic criteria.

Cost-Effectiveness

What strategies for using carotid imaging are cost-effective?

The lack of good or consistent evidence regarding the accuracy of noninvasive carotid imaging strategies makes it

difficult to accurately determine the most cost-effective strategy for selecting patients with stroke for CEA. Assuming the accuracy of statistics derived from this review, two testing strategies provide the most benefit when compared to no testing: first, administer MRA and refer patients with severe (70–99 percent) stenosis directly to CEA. Second, administer joint CUS and MRA, and when both tests demonstrate moderate to severe (50–99 percent) stenosis, refer patients directly to CEA. When the two tests disagree, request angiographic confirmation. The incremental cost-effectiveness ratios for these two strategies are approximately $250,000 and $700,000 per QALY, respectively.

In sensitivity analyses, the variable with the greatest influence on the results of the carotid imaging model was the prevalence of severe carotid stenosis. At severe stenosis prevalences of 0.15 and below, all testing strategies were dominated by the strategy of no testing or had cost-effectiveness ratios exceeding $250,000 per QALY (0.15 was the prevalence assumed in the base-case analysis). However, as this prevalence increased above 0.15, the cost-effectiveness ratios of two strategies, CUS with angiographic confirmation of severe stenosis (CUS/Angio-70), and MRA with direct CEA referral for severe stenosis (MRA/70 percent), fell precipitously, such that at a prevalence of 0.20, these strategies had cost-effectiveness ratios in the range of $60,000 to $75,000 per QALY. At higher prevalences, these ratios fell further. When compared to the strategy of no testing, CUS/Angio-70 had an incremental cost-effectiveness ratio of less than $50,000 per QALY at a prevalence of 0.25, while the incremental cost-effectiveness of MRA/70 fell below $50,000 per QALY as the prevalence of severe stenosis approached 0.30. These results suggest that carotid imaging may compare unfavorably, in terms of cost-effectiveness, with other commonly endorsed health care interventions, when the prevalence of carotid stenosis is low. Carotid imaging may be most efficient for those with a high pretest probability of severe stenosis, e.g., patients with peripheral vascular disease or audible carotid bruits.

Varying the cost of testing did not substantively affect the results, except in the case where MRA was assumed to cost $2,500 (as opposed to $1,249 in the base-case analysis). In this analysis, the strategy of initial CUS with angiographic confirmation of severe stenosis became undominated, with a cost-effectiveness ratio of $280,000 per QALY. Varying the accuracy of the different testing strategies over wide ranges did not have a substantial overall effect on the results. When the perioperative complication rate was assumed to be zero, noninvasive strategies involving direct referral to CEA of patients with moderate or greater stenosis expectedly became the most cost-effective; without risk of complications, angiographic confirmation to avoid false positives was no longer beneficial, and the marginal benefit of CEA among patients with moderate stenosis was no longer counterbalanced by perioperative risk. Varying the duration of risk reduction associated with CEA between 2 and 10 years also did not substantively affect the cost-effectiveness ratios. Likewise, restricting the cohort to only patients with TIA or minor stroke, which reflects the patient populations in the two large carotid endarterectomy trials, did not have a major impact on cost-effectiveness ratios, though it did produce a different set of undominated strategies.

It is noteworthy that strategies in which patients with moderate (50–69 percent) stenosis were referred for CEA provided fewer QALYs than strategies in which such patients were treated nonsurgically, despite the fact that the review (and hence the model inputs) reflected an overall benefit from CEA for moderate stenosis. This occurred as a result of the fact that the benefit of CEA over nonsurgical management in patients with moderate stenosis is small, such that when a 3 percent discount rate is applied to account for the fact that health benefits incurred or realized in the future are considered to be of lower value than benefits realized in the present, the future benefits are outweighed by the perioperative complications incurred immediately after surgery. When perioperative complication rates were assumed to be zero, or when the discount rate was removed, strategies involving CEA for patients with moderate stenosis became more cost-effective.

Future Research

In the course of the review, several information gaps related to the effectiveness of echocardiography in the management of patients with stroke emerged. Most notable are the gaps in knowledge about the presence and degree of risk of stroke conveyed by echocardiographically identified lesions, and the efficacy of therapy in reducing that risk. Identifying the risk of recurrent stroke associated with echocardiographic lesions can be achieved through cohort studies of patients with and without these lesions, while the efficacy of treatment is best addressed through RCTs. Because RCTs can address recurrent stroke risk and treatment efficacy simultaneously, this study design would provide valuable information needed to establish the usefulness of echocardiography in stroke. Trials of anticoagulation for complex aortic atheroma and ASA (with and without PFO), lesions for which available evidence suggests an association with stroke and which are observed relatively frequently, may be the most appropriate for initial study. Some of these studies are already ongoing.

Additional studies that would help solidify the evidence related to echocardiography in stroke involve the accuracy and yield of echocardiography. Most studies of the accuracy of TTE in detecting LVT were conducted in the early 1980s, when echocardiography was still a relatively new technology. Newer studies assessing the accuracy of TTE in diagnosing

LVT as verified surgically or pathologically would provide helpful data for calculations of the effectiveness and cost-effectiveness of TTE in stroke patients. In addition, interobserver reliability should be assessed in these studies.

Further studies examining the yield of echocardiographic lesions on TTE and TEE would also add valuable information. Such studies would be most useful if consecutive stroke patients without AF were prospectively enrolled; if results were stratified by age, presence or absence of carotid artery stenosis, presence or absence of manifest cardiac disease, and stroke subtype and location; and if studies were conducted in community-based settings, preferably across multiple centers. This type of study would require collaboration across institutions, but data collection may be facilitated by the presence in some centers of stroke registries and registries of patients undergoing echocardiography.

Finally, studies establishing the complication rates of TEE in patients with stroke are needed. Because patients with stroke often have swallowing difficulties as well as coexisting heart disease, TEE-associated complications may occur more frequently in patients with stroke than in other patients. The harms associated with TEE must be accurately quantified in order to assess its overall utility.

Future economic evaluations would benefit from more accurate estimates of the cost of both TTE and TEE. While charges for these two tests, as assessed by Medicare, are similar, the actual cost of TEE may be substantially higher than that of TTE, due to the cost of additional time, equipment, and personnel required for TEE. Microcosting studies may help clarify the cost of these additional expenditures.

While additional research on diagnostic accuracy, including studies that either eliminate or adjust for verification bias, may help to clarify the accuracy of CUS, the finding that accuracy may vary from center to center suggests that it may not be possible to establish a generalizable estimate of CUS sensitivity and specificity. It may be more fruitful to conduct studies examining the factors (e.g., technical experience, quality management programs) that allow some centers to achieve higher CUS accuracy than others.

High-quality studies of MRA accuracy and reliability, particularly for contrast-enhanced MRA, both alone and in combination with CUS, are needed. Such studies should prospectively image consecutive patients with stroke and angiographically verify the presence or absence of stenosis in all patients; if this is not possible, a random sample of patients with negative MRA should undergo angiography for the purpose of adjusting for verification bias. Multicenter studies would be helpful in limiting the potential influence of publication bias and in clarifying the variability of accuracy across centers.

Studies of CEA complications indicate that complication rates are highly variable. Collaborative studies assessing the sources of this variability and potential interventions to reduce it, as has been done for coronary artery bypass graft surgery, may improve the quality of operative care and thereby improve the effectiveness of all strategies for carotid imaging.

Trials assessing the efficacy and safety of early versus late CEA would help in determining the most appropriate timing of carotid imaging. If early CEA (e.g., within 1 week of initial symptoms) were found to be as safe as delayed CEA, early recurrent strokes (within 30 days of symptom onset) might be avoided, thereby increasing the efficacy of CEA. If this were the case, the effectiveness of carotid imaging might be maximized when done shortly after initial presentation.

In addition to these recommended clinical studies, future economic evaluations of carotid imaging strategies would benefit from comparisons of the outcomes of CEA with those of the latest nonsurgical treatments for carotid stenosis. This would inform the issue of the appropriate comparator to CEA. Furthermore, economic evaluations would benefit from improved data on the epidemiology of recurrent stroke, the prevalence of moderate and severe carotid stenosis, and the relative benefits of CEA versus non-surgical management across clinical and demographic patient subgroups. Finally, new studies are needed of the costs and benefits of carotid imaging strategies beyond their use in decisionmaking about CEA, e.g., the potential value of information from carotid imaging in the diagnosis and treatment of cardiac disease.

Availability of Full Report

The full report from which this summary was derived was prepared for AHRQ by the Oregon Health & Science University Evidence-based Practice center under contract number 290-97-0018. Printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 49, *Effectiveness and Cost-Effectiveness of Echocardiography and Carotid Imaging in the Management of Stroke*. When available, Internet users will be able to access the report online through AHRQ's Web site at: www.ahrq.gov.

AHRQ Pub. No. 02-E021
July 2002
ISSN 1530-440X