Diagnostic Accuracy of Magnetic Resonance Angiography for Internal Carotid Artery Disease

A Systematic Review and Meta-Analysis

Sarah M. Debrey, BA; Hua Yu, MD; John K. Lynch, DO, MPH; Karl-Olof Lövblad, MD; Violet L. Wright, RN; Sok-Ja D. Janket, MD, MPH; Alison E. Baird, FRACP, PhD

Background and Purpose—Accurate diagnosis of the degree of internal carotid artery (ICA) stenosis is needed for decisions regarding optimal stroke prevention. Noninvasive magnetic resonance angiography (MRA) is being proposed and used as a replacement for the gold standard, intra-arterial angiography. Our purpose was to perform a systematic review and diagnostic meta-analysis to determine the sensitivity and specificity of time-of-flight (TOF) MRA and contrast-enhanced (CE) MRA for the detection of (1) high-grade (≥70% to 99%) ICA stenoses; (2) ICA occlusions; (3) moderately severe (50% to 69%) ICA stenoses; and (4) compare the overall accuracy of the 2 MRA techniques.

Methods—The medical literature on MRA and the diagnosis of ICA steno-occlusive disease was reviewed through the PubMed, EMBASE, and SCOPUS databases. All publication years were included through to November 2006. Studies were eligible for inclusion if they compared the accuracy of TOF or CE MRA for the detection of ICA disease against intra-arterial angiography and reported sufficient data.

Results—The overall sensitivity of TOF MRA for the detection of ≥70% to 99% ICA stenoses was 91.2% (95% CI: 88.9% to 93.1%) with a specificity of 88.3% (86.7% to 89.7%), whereas the sensitivity of CE MRA was 94.6% (92.4% to 96.4%) with a specificity of 91.9% (90.3% to 93.4%). For the detection of ICA occlusions, the sensitivity of TOF MRA was 94.5% (91.2% to 96.8%) and the specificity was 99.3% (98.9% to 99.6%), whereas the sensitivity and specificity values for CE MRA were 99.4% (96.8% to 100%) and 99.6% (99.2% to 99.9%), respectively. For moderately severe (50% to 69%) stenoses, TOF MRA had a sensitivity of only 37.9% (29.3% to 47.1%) and a specificity of 92.1% (89.6% to 94.1%); for CE MRA, the pooled sensitivity value was somewhat better at 65.9% (57.0% to 74.0%), whereas the specificity was 93.5% (91.3% to 95.3%).

Conclusions—TOF MRA and CE MRA showed high accuracy for the detection of high-grade ICA stenoses and occlusions with CE MRA having the edge over TOF MRA, but had only poor (TOF MRA) to fair (CE MRA) sensitivity for the detection of moderately severe stenoses. (Stroke. 2008;39:2237-2248.)

Key Words: carotid arteries ■ carotid artery stenosis ■ magnetic resonance angiography ■ angiography ■ contrast-enhanced magnetic resonance angiography

Because stroke is the third leading cause of death and the principal cause of disability in America, the public health implications for its prevention are monumental. In particular, with the aging of the United States population rising rapidly, stroke rates are expected to increase substantially over the next decade. Atherosclerotic internal carotid artery disease (ICAD) is responsible for many ischemic strokes (estimates range from 20% to 40%) and a significant proportion of transient ischemic attacks.

The accurate diagnosis of stenotic and occlusive ICAD is essential for determining which surgical or medical interventions should be used for primary and secondary stroke prevention. Carotid endarterectomy (CEA) is the most commonly performed surgery for the treatment of atherosclerotic ICAD with over 600,000 surgeries performed between 2000 and 2005 in nonfederal US hospitals. In patients with symptomatic high-grade (70% to 99%) internal carotid artery (ICA) stenoses, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported an absolute reduction in the risk of stroke at 2 years of 17% after CEA relative to medical therapy; the European Carotid Surgery Trial (ECST) reported an 11.6% absolute risk reduction at 5 years in patients with moderate and high-grade stenoses. In the NASCET trial, there was also some benefit of CEA in...
patients with moderate (50% to 69%) stenoses: symptomatic patients with 50% to 69% ICA stenoses had an absolute risk reduction of stroke of 4.6% at 5 years. Furthermore, in the Asymptomatic Carotid Atherosclerosis Study, asymptomatic patients with 60% to 99% stenoses showed a modest benefit from CEA. Similar results were obtained in patients with asymptomatic 60% to 99% stenoses randomized to either immediate or deferred CEA. Based on these figures, CEA is recommended for the secondary prevention of stroke in patients with high-grade stenoses and after consideration of other clinical factors for many with moderate-grade stenoses and also some with asymptomatic disease. Carotid artery stenting may be an alternative to CEA in patients who are at very high surgical risk.

Intra-arterial angiography (IAA), most commonly performed using digital subtraction angiography (DSA), is considered the gold standard technique for evaluating the presence and extent of ICAD. The stenosis grades used in the NASCET and ECST trials were determined by IAA. However, IAA is invasive, costly, and has risks that include an approximate 4% risk of transient ischemic attack and a 1% risk of disabling stroke or death. Because of these risks, there have been increasing calls for noninvasive screening methods for ICAD. In many hospitals, noninvasive imaging methods such as ultrasound, magnetic resonance angiography (MRA) and computed tomography angiography, either alone or in combination, are already being used to screen and select patients for CEA. Ultrasound is affordable and readily available, but the images produced by ultrasound are often lower in quality than that of computed tomography angiography or MRA and the accuracy is highly operator-dependent.

MRA has become widely used as a noninvasive diagnostic imaging modality for ICAD. It avoids the radiation and iodinated contrast exposure associated with computed tomography angiography. The first MRA method, phase-contrast MRA, was developed in the 1980s and was quickly followed by 2-dimensional (2D) and 3-dimensional (3D) time-of-flight (TOF) MRA. TOF MRA has been widely adopted for an array of clinical indications but is relatively insensitive to slow flow and is associated with long scan times and signal voids, all of which can lead to poor-quality imaging and overestimation of stenoses. More recently, contrast-enhanced (CE) MRA has been introduced. CE MRA produces high-quality images in a very short period of time and may alleviate some of the drawbacks associated with TOF MRA. Yet, to be a useful method for studying ICAD, the accuracy of MRA is imperative, because decisions regarding optimum stroke prevention depend on the results obtained. Of particular importance are the potential overcall of stenosis grade and the differentiation of high-grade stenosis from occlusion (occlusions not usually being amenable to surgery) and the accurate diagnosis of moderate-grade (50% to 69%) stenosis for the patient to receive optimal management.

Despite the rapid technological advances in MRA and a large radiological literature, there has been little systematic evaluation of its diagnostic accuracy. The one prior meta-analysis included a select population of symptomatic patients studied up to April 2004, and data for moderate-grade stenoses were available in a very small number of patients only. Our purpose was to provide an update and determine the sensitivity and specificity of TOF MRA and CE MRA for the detection of (1) high-grade (70% to 99%) ICA stenoses; (2) ICA occlusions; (3) moderately severe (50% to 69%) ICA stenoses; and (4) to compare the overall accuracies of the 2 MRA techniques using IAA as the gold standard.

Materials and Methods

Data Sources

The medical literature on MRA and diagnosis of ICA stenosis was reviewed through a variety of databases. Searches were run by 2 of the reviewers (SMD and AEB) using PubMed, Embase, SCOPUS, and the Cochrane Controlled Trials Register. All publication years were included with the search being performed for all papers published through to November 2006. PubMed was searched using medical subject headings terms and from the papers identified using these terms, reference lists were searched to identify any additional articles. No initial limits were set in this search, although only papers published in English were accepted. The Cochrane Controlled Trials Register database, SCOPUS, and Embase were all searched using particular keywords, described subsequently. Hand searches of selected papers’ references as well as recent publications of several key journals, including Stroke, Neurology, Circulation, and Radiology, were performed. Two independent searches were performed, one for TOF MRA and one for CE MRA. However, the key words and medical subject headings terms searched were the same, because both TOF and CE MRA can be searched with identical terms. By performing separate searches for forms of MRA, the researchers were able to accurately exclude papers according to specific criteria. The medical subject headings terms were carotid arteries, carotid stenosis, magnetic resonance angiography, and angiography. The key words were carotid artery, carotid artery stenosis, magnetic resonance angiography, contrast-enhanced magnetic resonance angiography, and angiography. Although other search terms exist in Embase and Scopus, it was found that the terms used were thorough and sufficient, due to the large quantity of results, in addition to the high overlap of papers found using different search terms. Hand searches of relevant journals resulted in complete concordance with the online databases, thereby validating these database searches as comprehensive and complete. During the initial search strategy, over 11,000 papers (duplicates included) were identified using 3 online databases (8231 with PubMed, 1209 with Embase, and 2119 with SCOPUS). The titles of all articles obtained were screened, and all abstracts of possible articles were further screened. Papers with abstracts that clearly fitted into a category for exclusion or diagnostic tests for medical conditions unrelated to cerebrovascular disease were eliminated at this level of the search before a full text was printed. After search completion, independent readers checked for agreement. On identification of a possible abstract for inclusion, the full text of the article was read and assessed for inclusion. In our search, there were no possible abstracts lacking full text versions. Any disagreements over article inclusion were solved by discussion. The search protocol is provided in Figure 1.

Study Selection

Inclusion Criteria

Studies were eligible for inclusion if they (1) evaluated the accuracy of 2D and/or 3D TOF MRA and/or CE MRA for the diagnosis of ICA stenosis (with or without data on occlusion) against the gold standard of IAA; (2) reported sufficient data to construct a 2×2 table of test performance; (3) conformed to the Standards for Reporting of Diagnostic Accuracy criteria; and (4) had image evaluations performed by blinded observers. Due to the limited number of studies published on this topic, all study designs were included (Tables 1 and 2). Papers that included only symptomatic patients were included and evaluated separately in the subgroup analyses. The QUADAS tool for evaluating the quality of included studies was performed separately by 2 blinded observers, and disagreements were resolved by consensus.
compared with those with 0% to 69% stenosis and 100% stenosis (ie, occlusions); (2) to evaluate ICA occlusion (nonoperative), patients with occlusion were compared with those with 0% to 99% stenosis; and (3) to evaluate moderate-grade ICA stenosis (potential operative candidates), patients with 50% to 69% stenosis were compared with those with 0% to 49% and 70% to 100% stenosis.

### Study Quality
Study quality was evaluated by examining the following criteria: duration of time between imaging procedures, prospective/retrospective design, number of subjects involved, the number of symptomatic versus asymptomatic patients, setting of study, blinding of readers, and whether subjects were consecutive (ie, as opposed to sporadic).

### Data Synthesis
The diagnostic accuracy of MRA in comparison to IAA was assessed by sensitivity and specificity values, receiver operator characteristic (ROC) curves, and positive and negative likelihood ratios. MetaDiSc software was used to generate pooled sensitivities and specificities and summary ROC plots. In this fixed effects modeling approach, each study was assigned a weight dependent on the number of arteries analyzed in that study. The degree of heterogeneity between studies was reported using the Cochran $\chi^2$ (Cochrane Q) statistic. When this value was divided by the degrees of freedom (number of studies minus 1), a value of greater than 1 is indicative of heterogeneity. When this value was found to be statistically significant, causes of heterogeneity were examined; sources of heterogeneity were also explored when Q(degrees of freedom was found to be greater than 1 but not statistically significant. In interpreting the ROC plots, an ROC curve for an inconclusive test will have a flatter slope and will lie closer to the diagonal line as it rises, whereas the ROC line of a perfect diagnostic test will have a very steep ascent because both sensitivity and specificity are equal to 100%. In clinical practice, it is suggested that a positive likelihood ratio of greater than 10 or a negative likelihood ratio less than 0.1 support high diagnostic accuracy for the respective test. Because likelihood ratios, diagnostic ORs, and summary ROC curves take into account both the sensitivity and specificity data, and therefore illustrate any tradeoffs that may occur, these values are considered to be more valuable in terms of diagnostic accuracy than a pooled, weighted value for sensitivity and specificity.

### Results
Included Studies
After the initial screening period, 72 papers investigating TOF MRA and 24 papers investigating CE MRA, some overlapping, were selected for further screening. Of these papers, 37 TOF MRA and 21 CE MRA papers fulfilled the inclusion criteria (Tables 1 and 2). Of the TOF papers, 11 used 2D TOF MRA, 14 used 3D TOF MRA, and 12 included both 2D and 3D TOF data (Table 1). For TOF MRA, there were 1651 subjects, whereas for CE MRA, there were 1047 subjects. Reasons for exclusion between primary and secondary screening included: duplicate data (5 TOF), poor quality (4 TOF), failure to use conventional angiography as the gold standard (4 TOF), data not provided/failed attempts to locate data (11 TOF MRA, 3 CE MRA), and other reasons, including papers only investigating intracranial stenoses or unrelated subject matter (12 TOF). The NASCET criteria for the grading of stenoses were used in the majority of studies; ECST criteria were used in 2 of 37 TOF MRA studies and one of 21 CE MRA study; in 11 early TOF MRA studies (before 1995), the method of stenosis measurement was not described. In one CE MRA study, the method of

### Data Extraction

#### Measurement of Stenosis
In the majority of the studies after 1995, the degree of ICA stenosis was measured using either NASCET guidelines (in which the grade of the stenotic lesion is determined relative to a segment of distal disease-free ICA) or ECST guidelines (where the grade of the stenotic lesion is compared relative to what the original ICA arterial outline would have been at the point of maximum stenosis); a 70% ECST stenosis is approximately equivalent to a 50% NASCET stenosis. The ECST measurements in this meta-analysis were not corrected to NASCET measurements; therefore, because this contributes to heterogeneity in the study, a subgroup analysis was performed in which the ECST papers were excluded. After final selection of included papers, data were extracted to form 2×2 tables of diseased and nondiseased vessels as seen on MRA using conventional angiography as the gold standard. The following comparisons of stenosis grades were performed: (1) to evaluate high-grade stenoses, patients with $\geq$70% to 99% ICA stenosis (ie, operative candidates) were compared with those with 0% to 69% stenosis and 100% stenosis (ie, occlusions); (2) to evaluate ICA occlusion (nonoperative), patients with occlusion were compared with those with 0% to 99% stenosis; and (3) to evaluate moderate-grade ICA stenosis (potential operative candidates), patients with 50% to 69% stenosis were compared with those with 0% to 49% and 70% to 100% stenosis.

For PubMed, the three searches were entered as follows:
1) carotid arteries [MeSH terms] AND magnetic resonance angiography [MeSH terms]
2) carotid stenosis [MeSH terms] AND magnetic resonance angiography [MeSH terms]
3) carotid arteries [MeSH terms] AND angiography [MeSH terms]

For Embase and Scopus, the two searches used were:
1) 'carotid artery' AND 'magnetic resonance angiography'
2) 'carotid artery stenosis' AND magnetic resonance angiography
3) carotid arteries [MeSH terms] AND angiography [MeSH terms]

Figure 1. Literature search strategy.
measurement was not reported. Less than half of these studies were prospectively carried out or were conducted in unselected populations. Only 12 of 37 TOF MRA and 5 of 21 CE MRA papers had sample sizes ≥50 subjects. Of the 37 TOF papers, 26 defined high-grade stenosis as 70% to 99%, 5 as 60% to 99%, 2 as 75% to 99%, and 4 as 80% to 99% (Table 1). Of the 21 CE MRA papers included in this analysis, 18 defined high-grade stenosis as 70% to 99% (Table 1).

### Table 1. Included TOF MRA Papers

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Type of TOF</th>
<th>Population</th>
<th>Prospective?</th>
<th>Consecutive Patients?</th>
<th>Time Between MRA and DSA</th>
<th>Definition of High-Grade Stenosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anzalone</td>
<td>2005</td>
<td>49</td>
<td>3D</td>
<td>Symptomatic</td>
<td>Yes</td>
<td>Yes</td>
<td>48 hours</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Fellner</td>
<td>2005</td>
<td>21</td>
<td>3D</td>
<td>Prescreened with ultrasound</td>
<td>No</td>
<td>Yes</td>
<td>14 days</td>
<td>&gt;80%†</td>
</tr>
<tr>
<td>DeMarco</td>
<td>2004</td>
<td>51</td>
<td>2D</td>
<td>Prescreened with ultrasound or symptomatic</td>
<td>No</td>
<td>Not stated</td>
<td>Not stated</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Scarabino</td>
<td>2003</td>
<td>23</td>
<td>3D</td>
<td>Clinical signs of CVI</td>
<td>Not stated</td>
<td>Yes</td>
<td>24 hours</td>
<td>&gt;80%†</td>
</tr>
<tr>
<td>Nederkoorn</td>
<td>2002</td>
<td>203</td>
<td>3D</td>
<td>186 of 203 symptomatic</td>
<td>Not stated</td>
<td>Yes</td>
<td>1 month</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Patel</td>
<td>2002</td>
<td>47</td>
<td>2D</td>
<td>Symptomatic</td>
<td>Yes</td>
<td>Yes</td>
<td>24 hours</td>
<td>&gt;80%†</td>
</tr>
<tr>
<td>Binaghi</td>
<td>2001</td>
<td>19</td>
<td>2D</td>
<td>Prescreened with DSA</td>
<td>Not stated</td>
<td>Yes</td>
<td>24 hours</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Johnson</td>
<td>2000</td>
<td>40</td>
<td>3D</td>
<td>Symptomatic</td>
<td>Yes</td>
<td>Not stated</td>
<td>Not stated</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Back</td>
<td>2000</td>
<td>40</td>
<td>2D</td>
<td>Referred for CEA</td>
<td>No</td>
<td>No</td>
<td>Not stated</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>Elgersma</td>
<td>2000</td>
<td>38</td>
<td>3D</td>
<td>Prescreened with ultrasound and symptomatic</td>
<td>No</td>
<td>Not stated</td>
<td>2 days</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Serfaty</td>
<td>2000</td>
<td>33</td>
<td>3D</td>
<td>Half symptomatic</td>
<td>Yes</td>
<td>Yes</td>
<td>Not stated</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Modaresi</td>
<td>1999</td>
<td>50</td>
<td>3D</td>
<td>Referred for CEA</td>
<td>Not stated</td>
<td>No</td>
<td>Not stated</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Sardanelli</td>
<td>1999</td>
<td>32</td>
<td>2D and 3D</td>
<td>Symptomatic</td>
<td>Not stated</td>
<td>Yes</td>
<td>7 days</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Ozaki</td>
<td>1999</td>
<td>29</td>
<td>3D</td>
<td>Some symptomatic</td>
<td>No</td>
<td>No</td>
<td>Not stated</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Scarabino</td>
<td>1998</td>
<td>64</td>
<td>2D and 3D</td>
<td>Clinical signs of CVI</td>
<td>Not stated</td>
<td>Yes</td>
<td>24 hours</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Magarelli</td>
<td>1998</td>
<td>20</td>
<td>3D</td>
<td>Symptomatic, referred for DSA</td>
<td>Not stated</td>
<td>Not stated</td>
<td>3 days</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Jackson</td>
<td>1998</td>
<td>50</td>
<td>2D</td>
<td>Prescreened with ultrasound, referred for DSA</td>
<td>Yes</td>
<td>Yes</td>
<td>21 days</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Strotzer</td>
<td>1998</td>
<td>40</td>
<td>3D</td>
<td>Suspected ICAD</td>
<td>Not stated</td>
<td>Yes</td>
<td>Not stated</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Huston</td>
<td>1998</td>
<td>50</td>
<td>2D and 3D</td>
<td>Referred for DSA</td>
<td>Yes</td>
<td>Yes</td>
<td>2 weeks</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Fellner</td>
<td>1997</td>
<td>31</td>
<td>2D and 3D</td>
<td>Prescreened with ultrasound</td>
<td>Yes</td>
<td>Not stated</td>
<td>Not stated</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Patel</td>
<td>1995</td>
<td>88</td>
<td>2D and 3D</td>
<td>74 of 88 symptomatic</td>
<td>Yes</td>
<td>Not stated</td>
<td>Not stated</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Nicholas</td>
<td>1995</td>
<td>40</td>
<td>2D</td>
<td>Prescreened with ultrasound and DSA</td>
<td>No</td>
<td>Not stated</td>
<td>Not stated</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Dadachanji</td>
<td>1995</td>
<td>20</td>
<td>2D</td>
<td>Clinical signs of CVI</td>
<td>Not stated</td>
<td>Yes</td>
<td>Not stated</td>
<td>&gt;70%‡</td>
</tr>
<tr>
<td>Vanninen</td>
<td>1995</td>
<td>65</td>
<td>3D</td>
<td>55 of 65 referred for DSA</td>
<td>Not stated</td>
<td>Yes</td>
<td>1 day to 2 months</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Young</td>
<td>1994</td>
<td>70</td>
<td>2D and 3D</td>
<td>Symptomatic</td>
<td>Yes</td>
<td>Yes</td>
<td>2 to 3 weeks</td>
<td>&gt;70%‡</td>
</tr>
<tr>
<td>DeMarco</td>
<td>1994</td>
<td>20</td>
<td>2D and 3D</td>
<td>Referred for DSA</td>
<td>Yes</td>
<td>Yes</td>
<td>3 days</td>
<td>&gt;70%‡</td>
</tr>
<tr>
<td>White</td>
<td>1994</td>
<td>60</td>
<td>2D</td>
<td>Symptomatic</td>
<td>Yes</td>
<td>Yes</td>
<td>Within days</td>
<td>&gt;60%‡</td>
</tr>
<tr>
<td>Mittl</td>
<td>1994</td>
<td>38</td>
<td>2D</td>
<td>Clinical signs of CVI</td>
<td>No</td>
<td>Not stated</td>
<td>Not stated</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Sitzer</td>
<td>1993</td>
<td>50</td>
<td>2D</td>
<td>Prescreened with ultrasound and symptomatic</td>
<td>Yes</td>
<td>Yes</td>
<td>2 to 43 days</td>
<td>&gt;70%‡</td>
</tr>
<tr>
<td>Turnipseed</td>
<td>1993</td>
<td>30</td>
<td>2D</td>
<td>Symptomatic</td>
<td>Yes</td>
<td>Yes</td>
<td>Not stated</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Chiesa</td>
<td>1993</td>
<td>63</td>
<td>3D</td>
<td>Prescreened with ultrasound and symptomatic</td>
<td>Yes</td>
<td>Yes</td>
<td>Not stated</td>
<td>&gt;60%‡</td>
</tr>
<tr>
<td>Huston</td>
<td>1993</td>
<td>50</td>
<td>2D</td>
<td>Symptomatic, referred for DSA</td>
<td>Yes</td>
<td>Yes</td>
<td>Same day</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Anson</td>
<td>1993</td>
<td>20</td>
<td>2D</td>
<td>Symptomatic</td>
<td>No</td>
<td>Not stated</td>
<td>Less than 2 weeks</td>
<td>&gt;75%‡</td>
</tr>
<tr>
<td>Pan</td>
<td>1992</td>
<td>34</td>
<td>2D and 3D</td>
<td>Symptomatic</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>&gt;60%‡</td>
</tr>
<tr>
<td>Furuya</td>
<td>1992</td>
<td>22</td>
<td>3D</td>
<td>Suspected ICAD</td>
<td>No</td>
<td>Not stated</td>
<td>Not stated</td>
<td>&gt;60%‡</td>
</tr>
<tr>
<td>Mattle</td>
<td>1991</td>
<td>20</td>
<td>2D or 3D</td>
<td>13 of 20 symptomatic</td>
<td>No</td>
<td>Not stated</td>
<td>Not stated</td>
<td>&gt;70%‡</td>
</tr>
<tr>
<td>Kido</td>
<td>1991</td>
<td>31</td>
<td>2D</td>
<td>Suspected ICAD</td>
<td>No</td>
<td>Not stated</td>
<td>24 hours</td>
<td>&gt;80%‡</td>
</tr>
</tbody>
</table>

*NASCET measurement method used to determine stenosis grade except where stated.
†ECST method.
‡Method used to determine stenosis grade measurement not stated.
CVI indicates cerebrovascular insufficiency.
Detection of \( \geq 70\% \) to \( 99\% \) Internal Carotid Artery Stenoses

The results for \( 70\% \) to \( 99\% \) stenosis include the 32 of 37 TOF MRA and 19 of 21 CE MRA papers that reported results for \( \geq 70\% \) to \( 99\% \) stenoses, because these patients are operative candidates (Table 3). The results for pooled sensitivities and specificities for \( \geq 70\% \) to \( 99\% \) ICA stenosis are depicted in Figure 2A–D. The pooled sensitivities for TOF MRA and CE MRA for the detection of \( \geq 70\% \) to \( 99\% \) stenosis were 91.2\% (95\% CI: 88.9\%–93.1\%) and 94.6\% (92.4\%–96.5\%), respectively. The results for specificity were 88.3\% (86.7\%–89.7\%) for TOF MRA and 91.9\% (90.3\%–93.4\%) for CE MRA (Table 3). Summary ROC results are presented in Figure 3A–B.

Detection of Internal Carotid Artery Occlusions

Occlusion data were available in 29 of 37 TOF MRA studies and 18 of 21 CE MRA studies (Table 3). The sensitivity of TOF MRA for the detection of ICA occlusions was 94.5\%.

Table 3. Diagnostic Accuracy for \( \geq 70\% \) to \( 99\% \) ICA Stenosis, ICA Occlusion, and 50\% to 69\% ICA Stenosis

<table>
<thead>
<tr>
<th>Stenosis Level</th>
<th>TOF MRA</th>
<th>CE MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 70% ) to ( 99% )</td>
<td>Sensitivity, %</td>
<td>Specificity, %</td>
</tr>
<tr>
<td>Occlusion</td>
<td>91.2 (88.9–93.1)</td>
<td>88.3 (86.7–89.7)</td>
</tr>
<tr>
<td>50% to 69%</td>
<td>94.5 (91.2–96.8)</td>
<td>99.3 (98.9–99.6)</td>
</tr>
</tbody>
</table>

*Head-to-head comparison of TOF MRA and CE MRA in the same group of 172 subjects for the detection of \( 70\% \) to \( 99\% \) ICA stenosis.
(91.2% to 96.8%) with a specificity of 99.3% (98.9% to 99.6%), whereas the sensitivity of CE MRA was 99.4% (95% CI: 96.8% to 100%) with a specificity of 99.6% (99.2% to 99.9%). The positive and negative likelihood ratios of TOF MRA were 56.24 (38.87 to 81.36) and 0.12 (0.07 to 0.19). For CE MRA, these values were 80.5 (48.16 to 134.70) and 0.07 (0.04 to 0.13), respectively, again supporting a superior accuracy of CE MRA over TOF MRA for the detection of ICA occlusion. The corresponding summary ROC curves are shown in Figure 3C–D.

Detection of Moderate-Grade Internal Carotid Artery Stenoses 50% to 69%

Although it has been shown that CEA can be effective in symptomatic patients with 50% to 69% stenosis, very few papers published data on this level of stenosis. Only 7 of 37 TOF MRA and 8 of 21 CE MRA papers presented these data (Table 3; Figure 4). The 7 TOF papers resulted in a pooled sensitivity of only 37.9% (29.3% to 47.1%) and a pooled specificity of 92.1% (89.7% to 94.1%). The 8 CE MRA papers had a pooled sensitivity of 65.9% (57.0% to 74.0%) and a pooled specificity of 93.5% (91.3% to 95.3%).


Only 5 studies assessed both TOF MRA and CE MRA in the same subjects (n = 172) for the detection of high-grade steno-
ses,26,27,33,35,37 CE MRA was more accurate than TOF MRA with a higher sensitivity and a similar specificity to TOF MRA (Table 3). TOF MRA produced a pooled sensitivity of 89.6% (82.2% to 94.7%) and a pooled specificity of 92.7% (88.5% to 95.7%), whereas CE MRA produced a pooled sensitivity of 96.2% (90.5% to 99.0%) and a pooled specificity of 92.7% (88.6% to 95.7%).

Subgroup Analyses
To study the robustness of the results, a number of subgroups were analyzed in a sensitivity analysis. When the analyses were broadened to include the data from all of the included studies, according to each paper’s definition of “high-grade” stenosis, the results were very similar (Table 4) to those for ±70% to 99% stenosis. In case overcall of occlusion by MRA was not being detected in these analyses, a separate analysis was performed in patients with angiographic stenoses of 70% to 100%, but this gave essentially the same results (Table 4). The other sections of the sensitivity analyses include papers that studied high-grade stenosis detection in only symptomatic subjects as opposed to a population of symptomatic and asymptomatic patients and papers published after 2003 (Table 4). Both methods showed high accuracy for the detection of high-grade stenosis in symptomatic patients. Results for both MRA methods for high-grade stenosis were highly accurate for papers published after 2003.

As shown in Tables 1 and 2, some papers did not report the method of stenosis measurement. To decipher whether these studies, as well as the few studies that used ECST instead of NASCET methods, contributed to heterogeneous results, a sensitivity analysis was completed, including only those papers that explicitly stated the NASCET protocol was.
followed. Results for this subgroup were nearly identical to the overall analysis results for high-grade stenosis.

Discussion

The major findings of this systematic review and meta-analysis are (1) that MRA is highly accurate for the diagnosis of high-grade ICA stenoses and occlusion with both TOF and CE techniques, with CE MRA having the edge over TOF MRA; (2) that MRA is of high accuracy for distinguishing ICA occlusions from high-grade stenoses, particularly CE MRA; and (3) that both CE MRA and especially TOF MRA appear to be poor diagnostic tools for moderate ICA stenoses. It was also noted that despite the large literature on MRA, the data, the quantitative estimate of benefit of CE MRA over TOF MRA is that for every 30 MRA studies, one 70% to 99% stenosis would be detected on CE MRA that was missed on TOF MRA. Similarly, for every 20 MRA studies, an ICA occlusion would be detected on CE MRA that was missed on TOF MRA.

Variations in study design and reporting are significant sources of heterogeneity in a meta-analysis of this kind. Five major potential sources of heterogeneity were identified: (1) The lack of data in unselected populations is felt to be a major limitation of the studies in this meta-analysis. Many studies were restricted to patients with symptomatic ICA disease or those found to have a stenosis on screening with ultrasound. Optimal technology assessment, however, requires inclusion of individuals without the disease (ie, patients who are not symptomatic and those who do not have ICAD). (2) Two

### Table 4. Subgroup Analyses

<table>
<thead>
<tr>
<th></th>
<th>TOF MRA</th>
<th>CE MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies, N</td>
<td>Patients, N</td>
</tr>
<tr>
<td>All studies: high-grade stenosis‡</td>
<td>37</td>
<td>1651</td>
</tr>
<tr>
<td>Occlusion versus high-grade stenosis‡</td>
<td>26</td>
<td>1168</td>
</tr>
<tr>
<td>70% to 99% NASCET¶</td>
<td>23</td>
<td>1123</td>
</tr>
<tr>
<td>50% to 69% NASCET¶</td>
<td>6</td>
<td>394</td>
</tr>
<tr>
<td>Symptomatic§</td>
<td>27</td>
<td>1347</td>
</tr>
<tr>
<td>Publication &gt;2003</td>
<td>4</td>
<td>144</td>
</tr>
</tbody>
</table>

*Varially defined as 70% to 99%, 60% to 99%, 75% to 99%, 80% to 99%, or 50% to 99% stenosis.
†Analysis limited to patients with stenoses 70% to 100% to evaluate if overcall of high-grade stenosis was a limitation in the differentiation of high-grade ICA stenosis (ie, 70% to 99%) from ICA occlusion; data on stenoses <70% were dropped from this analysis.
‡Analysis limited to studies that used the NASCET method for stenosis measurement.
§Patients with symptomatic ICA disease.
further major sources of heterogeneity were the variation in (a) the methods used to measure stenosis grade, and (b) the number and types of stenosis grades that were reported as evidenced by the lack of data on moderate-grade stenoses. Evaluation of varying degrees of stenosis can result in suboptimal positive predictive values as evidenced in a recent study.76 The use of varying stenosis grade may explain why Wright et al77 was an outlier; this study also used a head and neck coil and hence evaluated ICA stenoses in a much wider field of view. (3) Although it was necessary to compare data from both CE MRA and TOF studies, the majority of the included TOF papers were published earlier than those investigating the accuracy of CE MRA. Approximately 76% of the CE MRA papers were published in the last 4 years compared with only 16% of the TOF papers. MRA is a relatively new technology with first reports of its clinical use being less than 25 years old and the rate of improvement in technological advancements and user reliability has been marked. Although it was believed that the dates of the studies would be a serious source of heterogeneity, the data proved otherwise with surprisingly high rates of sensitivity and specificity for TOF MRA over 10 years ago. (4) This apparent high degree of accuracy raises the question as to whether some of the earlier TOF MRA images were dropped from analysis due to poor imaging quality, thus giving the potential for selection bias in the TOF MRA studies, resulting in the overprojection of its accuracy. This issue was frequently discussed in the early MRA literature, because poor imaging quality, due to a variety of factors including patient movement, artifact, and slow flow, were common concerns with TOF MRA. In later years, technology and imaging technique improvements led to a decrease in these difficulties. The raw data in the 2×2 tables do not show this dilemma, because images graded as “nondiagnostic” quality are simply removed from the analysis before being compared with the corresponding IAA images. This was not as common an occurrence in the CE MRA studies; in the cases of blurred images due to patient motion or artifact, these images were more often included in the analyses. Other papers stated that the precise definition of stenosis was not always feasible with the TOF images due to flow voids or signal dropout. In these cases, a signal dropout was usually identified in these papers as a severe stenosis, which would alter the data dramatically on the topic of differentiating high-grade stenosis from occlusion. Signal dropout can be the result of many factors, including turbulent flow, patient movement, and other technical difficulties and may actually not be due to a high-grade stenosis. Regardless, imaging failure and the reporting of signal voids as a high-grade stenosis are limitations in early TOF studies and must be taken into account in the comparison of TOF MRA and CE MRA data in this meta-analysis. (5) The majority of TOF MRA studies used 3D TOF MRA; however, there are several studies that incorporated both 2D and 3D techniques. Although 3D is often considered a stronger diagnostic technique due to improved signal-to-noise ratio, in areas of slow flow it may be advantageous to use 2D instead of 3D TOF. Studies using both forms may be more complete, because transverse 2D images are more sensitive to slow flow and can therefore discriminate between critical stenosis (i.e., >95%) and occlusion. As can be seen from both the forest plots of sensitivity and specificity, as well as the ROC curves, more heterogeneity exists in the TOF MRA data than in the CE MRA data for high-grade stenosis. In particular, the CE MRA sensitivity plot shows very little heterogeneity. This could be due to a variety of factors and is most likely the result of similar study designs across these papers.

It should also be noted that publication bias may be a source of heterogeneity. It is possible that studies demonstrating poor accuracy of MRA as compared with IAA may not have been published. The accuracy of imaging results depends on the instruments and technology used as well as the experience of the operator and radiologist. Studies showing excellent concordance between MRA and IAA are most often performed in academic radiology departments. Therefore, results from centers with decreased quality control may be less optimistic and perhaps less likely to be published.

Differences in diagnostic threshold could potentially have contributed to heterogeneity in this analysis. It has been stated previously that differences in study design, including NASCET/ECST measurements and varying definitions of “high-grade” stenosis contribute to heterogeneity. However, it is possible for differences in diagnostic threshold to exist despite the use of the same diagnostic threshold such as defining 70% to 99% stenosis as severe. If a threshold effect is present, it can be visually interpreted through the ROC plots. Sensitivity will increase with decreasing specificity or vice versa. This is illustrated on the corresponding ROC plots, which, in this case, show weak evidence of diagnostic threshold, because both sensitivity and specificity increase simultaneously.

Only limited data were available for 50% to 69% stenoses; sometimes 30% to 69% stenosis data were reported, although such a large range of data is not useful for CEA decision-making.8 At present, many, but not all, patients with moderate-grade stenosis are referred for surgery after consideration of a number of clinical factors; patients with the best operative outcomes are male, those with hemispheric stroke or transient ischemic attack (as opposed to retinal ischemia), and those who do not have contralateral ICA occlusion. In cases of endovascular angioplasty or stenting, the results of noninvasive imaging will be de facto confirmed or rejected by IAA. Even with the limited data available, both CE MRA and especially TOF MRA appear to be poor diagnostic tools for moderate ICA stenosis. Their higher specificities only show that MRA is somewhat more accurate in ruling out the presence of a moderate stenosis. The cause of the reduced sensitivity may relate to image resolution. It is quite possible that some patients assessed as having high-grade stenosis on MRA, in fact, only have moderate-grade disease and vice versa, patients with moderate-grade disease may have high-grade disease. The potential clinical impact of these findings is most important for good clinical practice and will need to be considered and investigated as a matter of urgency.

This new information updates results obtained in the prior systematic reviews. MRA techniques have shown a continued evolution and improvement in their accuracy for the assessment of ICA stenoses. It is clear that many research centers and hospitals have already made the transition to noninvasive MRA as a sole imaging modality and determinant for CEA.
despite some reports that may demonstrate that MRA does not meet the threshold of diagnostic quality that would allow its independent use in all clinical settings, MRA has the advantages of being less expensive, less time-consuming, and noninvasive as compared with DSA. It is also capable of imaging vessels with unusual pathologies and produces stronger images of vessels not normally imaged with traditional noninvasive imaging, including the vertebral and subclavian arteries. Although the data for TOF MRA and CE MRA are fairly similar in this meta-analysis, especially for high-grade ICA stenoses and occlusions, there are other factors that must be taken into account. For instance, CE MRA unquestionably provides clearer, more defined images than TOF MRA. Also, because CE MRA is flow-independent, there is not a risk of signal void due to turbulent flow. Because TOF MRA appears to be in the process of being phased out in some centers, some studies have only looked at issues such as patient preference with CE MRA versus DSA. It has been found in a recent study that patients appear to prefer CE MRA over DSA. According to U-King-Im et al, 67% of subjects were willing to have a repeat MRA versus 41% for DSA.

In conclusion, from this meta-analysis, the current change to the use of MRA to detect high-grade ICA stenoses and occlusions appears justified with CE MRA having the edge over TOF MRA. However, the accuracy of MRA has yet to be proven for the detection of moderate-grade stenoses, and it is recommended that a second noninvasive study be obtained to confirm the grade of ICA disease at this time before treatment decisions are made. A complimentary diagnostic tool such as ultrasound or computed tomography angiography or DSA is necessary in these cases for decision-making regarding potential carotid endarterectomy or stenting. With over 660 000 CEAs performed in the United States over the past 5 years, there is a need for larger studies including both symptomatic and asymptomatic subjects with tighter study reporting of age data. Future studies should include patients with varying degrees of ICA stenosis severity, including mild stenoses. This work is also needed to confirm that the more expensive CE MRA, which the literature has shown to be largely replacing TOF MRA in recent studies, is truly a better diagnostic tool. It is essential that these studies be completed in a prospective and blinded fashion to fully answer the questions arising from this meta-analysis and systematic review and to ensure that each patient receives optimal care.

Sources of Funding
This research was supported in part by the Intramural Research Program of the NIH, NINDS. S.D.J. is supported by the National Scientist Development Grant from the American Heart Association.

Disclosures
None.

References
5. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. European Carotid Surgery Trialists’ Collaborative Group. Lancet. 1991;337:1325–1329.
...


Diagnostic Accuracy of Magnetic Resonance Angiography for Internal Carotid Artery Disease: A Systematic Review and Meta-Analysis
Sarah M. Debrey, Hua Yu, John K. Lynch, Karl-Olof Lövblad, Violet L. Wright, Sok-Ja D. Janket and Alison E. Baird

*Stroke*. 2008;39:2237-2248; originally published online June 12, 2008; doi: 10.1161/STROKEAHA.107.509877
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/39/8/2237

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/