Carotid Artery Imaging for Secondary Stroke Prevention
Both Imaging Modality and Rapid Access to Imaging Are Important

Joanna M. Wardlaw, FMedSci; Matt D. Stevenson, PhD; Francesca Chappell, MSc; Peter M. Rothwell, FMedSci; Jonathan Gillard, FRCS; Gavin Young, MD; Steven M. Thomas, FRCS; Giles Roditi, FRCS; Michael J. Gough, PhD

Background and Purpose—Patients with transient ischemic attack require carotid imaging to diagnose carotid stenosis. The differing sensitivity/specificity and availability of carotid imaging methods have created uncertainty over which noninvasive method is best and whether intra-arterial angiography is still required. We evaluated the influence of carotid imaging methods on secondary stroke prevention.

Methods—We modeled the effect of different carotid imaging strategies and timing on endarterectomy workload, stroke, and death at 1 and 5 years. We used all available data on stroke prevention after transient ischemic attack from systematic reviews (carotid imaging, medical and surgical interventions), population-based transient ischemic attack/stroke studies, government statistics, and stroke prevention clinics.

Results—Choice of imaging strategy affected speed of assessment, strokes prevented, and endarterectomy workload. The number of strokes prevented at 5 years varied by up to 22 per 1000 patients between imaging strategies for a given time to assessment. Delaying endarterectomy from 14 to approximately 30 days would fail to prevent up to 11 strokes per 1000 patients depending on the imaging strategy. Sensitive fast imaging (eg, ultrasound) was best for patients seen early; specific imaging (eg, CT angiography or contrast-enhanced MR angiography) was best for patients seen late after transient ischemic attack. Intra-arterial angiography conferred no advantage over noninvasive imaging.

Conclusions—Rapid access to sensitive noninvasive carotid imaging prevents most strokes. However, imaging strategies differ in their effect on stroke prevention by as much as 22 per 1000 patients and optimal imaging varies with time after transient ischemic attack TIA. Routine intra-arterial angiography should be avoided. (Stroke. 2009;40:3511-3517.)

Key Words: carotid arteries ▪ CT angiography ▪ imaging ▪ MR angiography ▪ prevention ▪ stroke ▪ TIA ▪ ultrasound

Patients with a transient ischemic attack (TIA) or minor stroke are at particularly high risk of disabling stroke, especially early after the TIA.1,2 Those with tight (70% to 99%) ipsilateral carotid stenosis require carotid endarterectomy.3 Some patients with moderate (50% to 69%) symptomatic stenosis also benefit from endarterectomy.4 Many patients with TIA do not have carotid stenosis requiring surgery, but all require some medical treatment. Stroke and TIA are common, so assessment and treatment should be efficient.

The association among carotid stenosis, stroke risk, and the effectiveness of endarterectomy was originally established using intra-arterial angiography (IAA).3,5 IAA is invasive, potentially hazardous,6 expensive, and not widely available. Therefore, most carotid imaging is now performed noninvasively with Doppler ultrasound, CT angiography (CTA), MR angiography (MRA) performed without exogenous contrast injection such as 2-dimensional or 3-dimensional time-of-flight methods, or contrast-enhanced MRA (CEMRA) performed dynamically after an intravenous bolus of gadolinium-based contrast.7 All of these, which we refer to collectively as “noninvasive imaging” to distinguish them from “invasive intra-arterial angiography,” are now very widely available, although access for patients with TIA varies between hospitals.8

Noninvasive carotid imaging is less accurate than IAA, particularly at 50% to 69% stenoses.9 Although switching from IAA to noninvasive imaging could reduce investigative risks, the net effect on endarterectomy workload and stroke prevention from less accurate stenosis measurement has not been determined. Differing availability of some noninvasive carotid imaging methods in some hospitals may incur delays to assessment, creating further uncertainty about how best to use the available modalities. A randomized trial large enough...
to compare IAA with noninvasive imaging for stroke prevention would be expensive, impractical, and probably unethical. Therefore, we modeled the effect of different carotid imaging strategies on endarterectomy workload and strokes prevented, including the effect of time to assessment, on stroke prevention at different times after TIA.

Methods

Study Design

We simulated the investigation and secondary prevention of stroke after TIA in a transition state model (Figure 1).10 This approach is particularly useful for diseases in which risk is ongoing over time, events may be recurrent, and their timing is important. Central to this methodology is the division of the given disease process into a finite number of mutually exclusive health states and the division of the relevant time horizon for the analysis into time increments. The distribution of patients across the health states over time is governed by transition matrices, which describe the probability of transitioning from the current health state to an alternative health state during each model cycle. Our model used the following health states: healthy, nonfatal stroke, fatal stroke, nonfatal myocardial infarction (MI), fatal MI, and death through other reasons. The model used time periods of variable length starting with 7 individual days, then 27 individual weeks, and then 4-weekly periods to 20 years to reflect the high initial stroke risk,11 which attenuates over time.4 We stratified short- and long-term stroke risk by carotid stenosis level.3 Patients allocated to endarterectomy had the same probabilities of stroke as similar patients not receiving endarterectomy until the endarterectomy, which reduced the subsequent risk of stroke but carried a risk of iatrogenic stroke, MI, or death. Deaths not related to stroke, surgery, or MI were modeled independent on age and sex12 adjusted so that deaths associated with stroke were not double-counted.

Participants

We derived a cohort of 100 patients, 51% of whom were assumed to be on aspirin at the time of the TIA.1,13 distributed into different age bands (55 to 64 years, 65 to 74 years, 75 to 84 years, and ≥85 years) and sex (male or female) assuming an age/sex mix equivalent to a typical west European country (www.statistics.gov.uk/census2001/pyramids/print/uk.asp). We estimated the annual incidence of TIA/ minor stroke by age/sex from the Oxford Vascular Study (OXVASC).13 which showed that a hypothetical population of 500 000 would have an estimated 490 incident minor strokes and TIA per annum. “Minor stroke” was defined as nondisabling (modified Rankin score of 0 to 2).

Each age and sex combination was subdivided into stenosis levels according to stenosis prevalence in a large stroke registry.14 Thus, 6% of patients would have a 70% to 99% stenosis, 4% would have a 50% to 69% stenosis, and 90% would have <50% stenosis (North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria).

Stroke Services

Stroke prevention services are evolving rapidly. We obtained baseline (“traditional”) representative stroke prevention clinic scenarios by surveying 17 large UK stroke centers. Most held stroke prevention clinics twice weekly and, saw 6 to 10 patients per clinic at between 1 and 21 days after TIA. Forty percent to 60% of patients were ultimately diagnosed as TIA/minor stroke.

Imaging

We devised a range of carotid imaging strategies (Table 1), including invasive and noninvasive methods (CTA, MRA, CEMRA, and ultrasound), reflecting their availability in clinics and focusing the decision points (eg, 50% stenosis) on those with the most data on accuracy.9,15 “Ultrasound” refers to color Duplex ultrasound. We use the term “MRA” to refer to techniques such as 2-dimensional or 3-dimensional time-of-flight MRA performed without the injection of contrast and “CEMRA” to refer to MRA performed after an intravenous injection of a gadolinium-containing contrast agent. We analyzed MRA and CEMRA separately in the model because their accuracy compared with IAA differs. We did not distinguish different CTA postprocessing techniques because there were too few data in the systematic review to justify this. All data on noninvasive imaging from all modalities were subjected to the same critical appraisal during the systematic review process; carotid stenosis measurements were standardized on NASCET method. We set the baseline strategy as: “initial test ultrasound; if 50% to 99% stenosis, proceed to IAA; if 70% to 99% then proceed to endarterectomy” because IAA is the reference standard used in the endarterectomy trials that relates stenosis to stroke risk and ultrasound is the most widely and longest available noninvasive technique. The other strategies varied the stenosis level at which any confirmatory imaging was done and used different combinations of initial and confirmatory imaging, and different symptomatic stenosis levels at which surgery would be offered. Sensitivities and specificities were derived from an up-to-date systematic review of the world literature and individual patient data meta-analysis9,15: 70% to 99% stenosis, sensitivity: ultrasound (US), 0.89; CTA, 0.76; MRA, 0.88; CEMRA, 0.94; specificity: US, 0.84; CTA, 0.94; MRA, 0.84; CEMRA, 0.93. Fewer data were available for milder stenoses and accuracy was poorer.9,15 The sensitivity and specificity of each
noninvasive modality influenced the patients’ diagnosed stenosis and whether they would be referred for endarterectomy.

**Effects of Surgical and Medical Secondary Prevention**

Endarterectomy reduces the absolute risk of ipsilateral ischemic stroke by 16% (70% to 99% stenosis) and 4.6% (50% to 69% stenosis) compared to medical therapy. The effects of endarterectomy on stroke prevention are as follows:

- **Absolute risk reduction in five year risk of stroke:**
  - 30% stenosis: 3.2% 3
  - 50%–69% stenosis: 4.6% 3
  - 70%–99% stenosis: 16.0% 3

- **Annual risk of stroke after successful surgery:** 2.3% 5, 17, 18

Medical therapy reduces the relative risk of stroke as follows:

- **Aspirin, first 3 months:** 23% 19
  - 3 months onward: 15% 20, 21
- **Dipyridamole:** 10% 21, 22
- **Antihypertensive (manifest from 6 months):** 10% 23
- **Statin (manifest from 12 months):** 25% 24

Combination medical therapy in combination (lower 95% CO of estimate of relative effect of medical therapies in combination)

- **First 3 months (mainly aspirin + dipyridamole):** 33% 25, 26
  - 3–6 months: 25% 25, 26
  - 6–12 months: 47% 25, 26
  - After 1 year: 55% 25, 26

Cumulative risk of stroke in patients on combination medical therapy

- **First week after TIA:**
  - 0%–49% stenosis: 7% 19–26
  - 50%–69% stenosis: 8% 19–26
  - 70%–99% stenosis: 13% 19–26

- **Second week to first month after TIA:**
  - 0%–49% stenosis: 9% 19–26
  - 50%–69% stenosis: 12% 19–26
  - 70%–99% stenosis: 19% 19–26

- **Second month to one year after TIA:**
  - 0%–49% stenosis: 20% 19–26
  - 50%–69% stenosis: 25% 19–26
  - 70%–99% stenosis: 39% 19–26

- **Second to third years after TIA:**
  - 0%–49% stenosis: 26% 19–26
  - 50%–69% stenosis: 33% 19–26
  - 70%–99% stenosis: 48% 19–26

*For the 51% of patients already on aspirin at the time of TIA, the relative risk reductions at 3 months onward were used for the first 3 months.
stenosis) with no increased risk of early versus late surgery (Table 2). The risk of stroke after successful carotid endarterectomy was set at 2.3% per annum (weighted average of available endarterectomy trial data). For medical treatment, we used data from all available randomized trials and systematic reviews (Table 2). We assumed that patients would be prescribed aspirin and dipyridamole, an antihypertensive, and a statin at presentation (Table 2). We used risk reductions at >3 months (15%) for those patients who were already on aspirin at the time of the TIA/MI minor stroke because they would have less absolute risk reduction from continuing to take aspirin than those starting de novo. Some patients might not receive medical or surgical treatment until some time after their TIA/minor stroke through delays in reaching medical attention. In the absence of control populations who remained truly untreated with all drugs and from whom we could extract the risk of events by degree of stenosis and time since TIA, we estimated the risk of stroke without medical treatment from the mean absolute risk of events on medical treatment19–24 divided by the point estimate of the relative risk reduction of that treatment. Unfortunately, few data were available on the combined efficacy of these drugs. They may work independently and additively, so a relative reduction in stroke of 75% could be obtained.25,26 In the absence of direct data for antihypertensives and statins, we used the lower 95% CIs for these therapies (Table 2).

Risk and Long-Term Outcome After Stroke or MI

The proportion of patients dying and surviving in a dependent or independent state after stroke, by Rankin score and age, was taken from a Stroke Registry and the OXVASC study with an overall case fatality after stroke of 13% (Table 2). The risk of death from all causes after stroke was increased 2.5-fold27 and of MI or cardiovascular death after a TIA/MI minor stroke was 27.8% at 10 years,17 which equates to 3.2% per annum. The probability of an MI being fatal ranged from 31% at age 55 to 64 years to 90% at age ≥85 years.28

Analysis

We estimated the number of endarterectomies in total and by stenosis band, surgical deaths, strokes (fatal and nonfatal, including iatrogenic strokes), and MI (fatal and nonfatal) per imaging strategy occurring by 28 days, 1 year, and 5 years per 100 patients with TIA/MI minor stroke based on “traditional” clinic timings. For epidemiological comparisons, we also expressed the results as “events per 1000 patients.” Sensitivity analyses were conducted on time from TIA/MI minor stroke to endarterectomy (14, 80, and 180 days after TIA/MI minor stroke). Further modeling data, including Markov traces, are provided at www.shef.ac.uk/scharr/sections/heds/staff/stevenson_m.html.

We checked that all studies contributing data to this analysis were covered for this purpose by their original ethics approvals.

Results

On “traditional” clinic timings, the average time from TIA to endarterectomy was 41 days. Ultrasound enabled the fastest times to endarterectomy (31 days) even when a second confirmatory ultrasound was performed (35 days; Table 1). Imaging strategies with CTA, MRA, or CEMRA achieved endarterectomy by 49 days even if only one imaging test was used due to their lesser availability. The worst delays occurred in patients requiring a third imaging test because the first 2 tests had disagreed, for example, 54 days or even 68 days.

In the baseline strategy, 5.9% of patients would be referred for endarterectomy. However, choice of imaging created a 5-fold variation in endarterectomy referral (Table 1; Supplemental Figure I, available at http://stroke.ahajournals.org) from 5.4% to 17.1% for strategies offering endarterectomy to 70% to 99% stenosis (12.8% to 26.7% in which patients with 50% to 99% stenosis had endarterectomy). The number of endarterectomies within each stenosis band also varied markedly between imaging strategies (Supplemental Figure I). Some strategies (generally those with relatively low imaging specificity at 0% to 49% stenosis, for example, US and MRA) resulted in large numbers of patients who actually had 0% to 49% stenosis being offered surgery because the noninvasive imaging classed them as having higher-grade stenoses. Surgical deaths ranged from 0.06% to 0.25% and were closely related to the number of endarterectomies (Supplemental Table I, available at http://stroke.ahajournals.org).

On “traditional” timings, the number of strokes per 100 patients with TIA per imaging strategy at 5 years ranged from 25.4 (US) to 26.9 (US and IAA; Figure 2), a difference of up to 15 per 1000 patients with TIA between imaging strategies. The strategies resulting in the fewest strokes were those in which patients reached endarterectomy most quickly (eg, US) and those offering rapid endarterectomy to 50% to 69% as well as 70% to 99% stenoses. The most strokes occurred with highly specific imaging (eg, CTA, CEMRA, IAA) because these offered endarterectomy to few patients outside the 70% to 99% stenosis group and strategies involving IAA because the risk of iatrogenic stroke was high.

Simply achieving endarterectomy by 14 days, instead of at “traditional” timings, prevented between 4 and 12 strokes per 1000 TIA at 1 year (2 to 11 strokes per 1000 TIA at 5 years) per imaging strategy (Figure 2). It also increased the difference between the imaging strategies; the difference between strategies for endarterectomy at 14 days was up to 22 strokes prevented per 1000 TIA at 5 years (12 per 1000 at 1 year). Increasing delays to endarterectomy prevented fewer strokes. Thus, depending on the imaging strategy, delaying endarterectomy from 14 to 180 days would typically fail to prevent up to 24 strokes per 1000 patients with TIA at 1 year and 25 per 1000 at 5 years (Figure 2).

Due to differences in the sensitivity and specificity of imaging methods, the optimal imaging strategy varied with time to endarterectomy. With endarterectomy by 14 days, high-sensitivity imaging (US) and offering endarterectomy to patients with 50% to 69% as well as 70% to 99% stenosis prevented most strokes at 1 and 5 years (Figure 2). However, if endarterectomy was delayed, there would be less benefit for patients with 0% to 69% stenosis due to their lower stroke risk, but with high-sensitivity imaging, large proportions would still be referred for endarterectomy with increased surgical deaths (Supplemental Table) and therefore an overall lower life expectancy. For patients reaching endarterectomy late, only those with 70% to 99% stenosis would benefit from endarterectomy and therefore highly specific imaging (US, MRA, CTA, or IAA) was best because these helped limit endarterectomy to only patients with 70% to 99% stenosis.

Discussion

This model shows that rapid patient triage through carotid imaging to endarterectomy and the choice of noninvasive carotid imaging modality both affect the number of strokes prevented after TIA/minor stroke. Therefore, the gradual replacement of IAA with noninvasive imaging, despite concerns about the latter’s accuracy, is beneficial. IAA for routine diagnosis of carotid stenosis is no longer required,
incurs risks and unacceptable delays, and should be avoided. Ultrasound achieved the fastest times to endarterectomy even when a second US was required to confirm the stenosis. The availability of CTA and CEMRA is increasing, although is still less available for stroke than is really needed to deliver routine frontline TIA investigation (approximately 10 to 15 hours per week just for the carotid imaging generated by a typical 500,000 population). Use of CTA and CEMRA would reduce the need for repeat examinations because, unlike US, the images from one examination can be crosschecked by multiple observers, although more patients have contraindications to CEMRA or CTA than to US, and may cost more. The problem of what to do about the loss of the reference standard of IAA, which has already largely happened in

Figure 2. Strokes per 100 patients with TIA/minor stroke by imaging strategy and time to endarterectomy at (A) 1 year and (B) 5 years after initial TIA.
routine TIA investigation, is a general problem caused by continually evolving imaging technologies with no ideal solution.

These results are important because the number of strokes prevented simply due to choice of imaging (up to 22 per 1000) is of a similar absolute order of magnitude to the effect of aspirin (20 to 30 per 1000 reduction) or of dipyridamole added to aspirin (14 per 1000 reduction). The model also indicates that inadvertently offering some patients with <50% stenosis endarterectomy prevents more strokes provided that endarterectomy is performed early after TIA. Both US and MRA tend to overestimate stenoses and thus provide benefit when surgery is performed early. However, when patients present late after TIA, highly specific imaging such as CEMRA or CTA is needed to ensure that only those with definite 70% to 99% stenosis receive endarterectomy.

The total referrals for endarterectomy (and the number in each stenosis band) varied from 5% to 27% of TIAs. The current average operation rate may be nearer 5% to 10%. Operating early on 50% to 69% as well as 70% to 99% stenoses appeared to prevent more strokes in the long term, but at the cost of many more endarterectomies, surgical complications, and increased morbidity. This could only be justified in patients reaching surgery early who were in high-risk groups.4

The strengths of this work include the collaboration between stroke clinical and imaging experts and modelers, the use of all available data to populate the model including up-to-date systematic reviews of the world literature, and the purpose-designed model reflecting timing of events after TIA. The limitations include the paucity of data for some parts of the model, for example, on many aspects of stroke risk and outcome, the effect of treatments in combination, and of imaging accuracy. We derived stroke risk in the absence of treatment from the absolute risk in medically treated patients divided by the relative risk reduction of each treatment. We assumed that the magnitude of combinations of medical treatments was additive but used conservative estimates.25

We used data mostly from studies in the United Kingdom because the data were current and available in the detail required in relevant populations. Country-specific differences in delivery of imaging and stroke services should be considered when translating these data outside Western Europe.8 The 22 imaging strategies were the most commonly used in the survey and remain relevant. Data were inadequate, both in the literature and in the individual patient analysis, to permit comparisons of the different ways of postprocessing CTA images or on minor variations in ways of performing US, MRA, or CEMRA.9,15 Data on imaging accuracy at 50% to 69% stenosis are very limited and may have affected the estimation of number of endarterectomies. The carotid endarterectomy trials were conducted in the 1980s and early 1990s, when fewer medical treatments were available so we may have exaggerated the benefit of endarterectomy compared with the maximum medical therapy now available. Alternatively, the benefit of endarterectomy may have been underestimated because the patients in the trials mostly did not reach endarterectomy until relatively late after TIA. Similarly, medical therapy was not implemented in many medical therapy trials until relatively late after TIA, so its benefit may have been underestimated.31 We may have underestimated the risk of stroke using IAA, because death from IAA may be >0.1% in elderly patients with stroke/TIA. We assumed that patients would reach each stage at rather fixed times, whereas the actual times would be more flexible. However, the relationships among imaging, endarterectomy, time, and stroke are unlikely to be influenced by increased variation in times to each stage.

The very high early risk of stroke after TIA has recently been emphasized.22,33 Very early treatment may prevent many of these strokes.31 Our study confirms the need for rapid assessment and treatment using data collected independently of the Early Use of Existing Preventive Strategies for Stroke Study.31 At “traditional” times, endarterectomy did not occur until on average 41 days after TIA, too late to prevent many of the strokes (>50% of those destined to have a stroke had already had the stroke by 14 days). An effect of similar order of magnitude to that of aspirin or dipyridamole on stroke prevention could be achieved simply by moving investigation and treatment into the first few days after TIA from “traditional timings.” Although many TIA clinics may now be assessing patients more quickly, persistent limited access to imaging and endarterectomy in many countries still may restrict stroke services.8 Hospitals should urgently review their TIA triage because cost-neutral reorganization of stroke, imaging, and surgical services rather than creating a new service can deliver substantial improvements (M. Hill, personal communication). Carotid imaging should be available 7 days per week with sufficient capacity to identify patients needing endarterectomy quickly from among the approximately 40% of patients referred to TIA clinics who do not have TIA/minor stroke and from the approximately 80% with TIA/minor stroke who do not need endarterectomy. Use of clinical scores such as ABCD3 and ABCD234 would help exclude non-TIAs, thus preserving limited scanner time for patients with a higher likelihood of carotid stenosis that would require endarterectomy.

Acknowledgments
We thank Professor Charles P. Warlow and Professor Martin Dennis for their helpful comments on the manuscript.

Sources of Funding
This project was funded by the UK National Health Service Research and Development Health Technology Assessment Programme reference number 01/37/03 and supported by the Scottish Funding Council (SFC) Brain Imaging Research Centre (www.sbir.esc.ac.uk). F.C. was supported by the Scottish Executive Chief Scientist Office (Ref No: CZF/1/23). J.M.W. is supported by the SFC through the SINAPSE Initiative (Scottish Imaging Network, A Platform for Scientific Excellence, www.sinapse.ac.uk), which also supports SBIRC. The study was designed, conducted, analyzed, and the manuscript written independently of all funders and the views expressed are those of the authors and not of the funders.

Disclosures
None.

References
ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ. 2004;328:326.


Carotid Artery Imaging for Secondary Stroke Prevention: Both Imaging Modality and Rapid Access to Imaging Are Important

Joanna M. Wardlaw, Matt D. Stevenson, Francesca Chappell, Peter M. Rothwell, Jonathan Gillard, Gavin Young, Steven M. Thomas, Giles Roditi and Michael J. Gough

Stroke. 2009;40:3511-3517; originally published online September 3, 2009;
doi: 10.1161/STROKEAHA.109.557017

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 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/40/11/3511

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/