Evidence Report

Stroke and Commercial Motor Vehicle Driver Safety

Presented to

The Federal Motor Carrier Safety Administration

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Prepared for

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Evidence reports are sent to the Federal Motor Carrier Safety Administration's (FMCSA) Medical Review Board (MRB) and Medical Expert Panels (MEP). The MRB and MEP make recommendations on medical topics of concern to the FMCSA.

The FMCSA will consider all MRB and MEP recommendations, however, all proposed changes to current standards and guidance (guidelines) will be subject to public notice and comment and relevant rulemaking processes.

Policy Statement

This report was prepared by ECRI Institute under subcontract to MANILA Consulting Group, Inc., which holds prime GS-10F-0177N/DTMC75-06-F-00039 with the Department of Transportation's Federal Motor Carrier Safety Administration. ECRI Institute is an independent, nonprofit health services research agency and a Collaborating Center for Health Technology Assessment of the World Health Organization. ECRI Institute has been designated an Evidence-based Practice Center (EPC) by the U.S. Agency for Healthcare Research and Quality. ECRI Institute's mission is to provide information and technical assistance to the healthcare community worldwide to support safe and cost-effective patient care. The results of ECRI Institute's research and experience are available through its publications, information systems, databases, technical assistance programs, laboratory services, seminars, and fellowships. The purpose of this evidence report is to provide information on the current state of knowledge on this topic. It is not intended as instruction for medical practice, nor for making decisions on individual patients.

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Executive Summary

Purpose of Evidence Report

Of all occupations in the United States, workers in the trucking industry experience the third highest fatality rate, accounting for 12 percent of all worker deaths. About two thirds of fatally injured truck workers are involved in highway crashes. According to statistics from the U.S. Department of Transportation (DOT), there were 4,932 fatal crashes involving a large truck in 2005 for a total of 5,212 fatalities. In addition, there were 137,144 non-fatal crashes; 59,405 of these were crashes that resulted in an injury to at least one individual (for a total of 89,681 injuries).

The purpose of this evidence report is to address several key questions posed by the Federal Motor Carrier Safety Administration (FMCSA). Each of these key questions was developed by the FMCSA so that the answers to these questions would provide information that would be useful in updating its current medical examination guidelines. The three key questions addressed in this evidence report are:

Key Question 1: Are individuals who have experienced a stroke at an increased risk for a motor vehicle crash (crash risk or driving performance)?

Key Question 2: If so, can neuropsychological testing of individuals who have experienced a stroke predict crash risk?

Key Question 3: Among individuals who have experienced a TIA (transient ischemic event), what is the risk of experiencing a future stroke?

Identification of Evidence Bases

Separate evidence bases for each of the key questions addressed by this evidence report were identified using a process consisting of a comprehensive search of the literature, examination of abstracts of identified studies in order to determine which articles would be retrieved, and the selection of the actual articles that would be included in each evidence base.

A total of seven electronic databases (MEDLINE, PubMed (PreMEDLINE), EMBASE, PsycINFO, CINAHL, TRIS, the Cochrane library) were searched (through January 10, 2008). In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant articles not identified by our electronic searches. Hand searches of the "gray literature" were also performed. Admission of an article into an evidence base was determined by formal retrieval and inclusion criteria that were determined *a priori.*

Grading the Strength of Evidence

Our assessment of the quality of the evidence took into account not only the quality of the individual studies that comprise the evidence base for each key question; we also considered the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Analytic Methods

The set of analytic techniques used in this evidence report was extensive. Random-effects meta-analyses were used to pool data from different studies. Differences in the findings of studies (heterogeneity) were identified using the Q-statistic and I^2. Sensitivity analyses, aimed at testing the robustness of our findings, included the use of cumulative random-effects meta-analysis.

Presentation of Findings

In presenting our findings we made a clear distinction between qualitative and quantitative conclusions and we assigned a separate strength-of-evidence rating to each conclusion format. The strength-of-evidence ratings assigned to these different types of conclusion are defined in Table 1.

Table 1. Strength-of-Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Minimally acceptable	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI recommends frequent monitoring of the relevant literature.
Insufficient	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI recommends frequent monitoring of the relevant literature.
Quantitative Conclusion (Stability of Effect Size Estimate)	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect in the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI recommends frequent monitoring of the relevant literature.

Evidence-Based Conclusions

Key Question 1: Are individuals who have experienced a stroke at an increased risk for a motor vehicle crash (crash risk or driving performance)?

Evidence suggests that drivers who have suffered a stroke are at an increased risk of crash. (Strength of Conclusion: Minimally Acceptable) The size of this risk could not be determined.

Direct Evidence – Crash Studies*: Current direct evidence from two of three crash studies found that individuals who have had a stroke are at an increased risk for a crash. The two studies that detected an increased risk of crash adjusted for miles driven; the study that did not find an increased risk of crash did not perform this adjustment. As risk exposure is the most important factor in determining risk, the findings of the two studies that adjusted for risk exposure should be given stronger consideration than the study that did not. The increased risk could not be quantified owing to differences in reporting. Limitations of the evidence supporting this conclusion are the small size of the evidence base (three studies) and overall low- to moderate-quality.*

Indirect Evidence – Studies of Driving Tests and Driving Simulation*: Two studies of on-road driving tests provide consistent but weak evidence suggesting that individuals who have suffered a stroke may be at increased risk for a motor vehicle crash because of their poor driving skills. The findings from two simulator studies conflict. Limitations of the evidence base include weakness of type of evidence (since it is indirect), small size of the evidence base, and overall low quality. In particular, controls may not have been well suited to drivers who had a stroke.*

The findings of the direct crash and on-road driving tests should be considered to supersede the simulator test findings because they provide more relevant information on crash risk than simulator studies.

Key Question 2: If so, can neuropsychological testing of individuals who have experienced a stroke predict crash risk?

Certain neuropsychological tests may predict the outcome of driving performance measured by a road test or in-clinic driving evaluation. (Strength of Conclusion: Moderate) Whether neuropsychological tests can predict actual crash risk cannot be determined from currently available evidence.

No studies provided direct evidence of an association between neuropsychological test results and crash risk. The only available indirect evidence evaluates neuropsychological tests as potential outcome predictors for road tests or in-clinic driving assessments. However, prediction of driving test outcomes is not the same as prediction of crash risk; patients who failed road tests or in-clinic driving assessments would either not be allowed to drive or at least advised not to drive, depending on the laws of the particular state or country of residence. Thus, they would not be expected to be at risk for motor vehicle crash (unless they disregard laws or advice). Whether

neuropsychological testing can identify stroke patients at increased risk of crash who were able to pass a road test has not been evaluated in the currently available literature.

***Indirect Evidence – Studies of Driving Performance**: Twelve studies (median quality: moderate) with 879 patients who had experienced stroke evaluated various neuropsychological tests as potential outcome predictors for road tests or in-clinic driving assessments. Eleven of the studies found that one or more neuropsychological tests were significant predictors of the outcome of road tests or driving evaluations in this patient population. These findings could not be combined in a quantitative analysis because no two studies used the same array of tests or evaluated the same combination of variables when attempting to identify predictors of outcome. However, certain tests were found to be significant outcome predictors in multiple studies. Figure of Rey was identified as a significant outcome predictor in three out of five studies that used it. The dot cancellation test, which is part of the Stroke Driver Screening Assessment (SDSA), was found to be a significant outcome predictor in four out of four studies. Another SDSA test (the Road Sign Recognition test) was found to be a significant outcome predictor in two out of four studies. A third SDSA test (What Else is in the Square test) was a significant outcome predictor in two out of three studies. Two out of three studies that used the Motor-Free Visual Perception Test (MVPT) identified it as a significant outcome predictor. Given the moderate quality of the studies and the consistency of the findings for neuropsychological tests overall, the strength of evidence supporting the ability of these tests to predict driving test outcomes is moderate.*

Since the majority of studies did not report the percentage of commercial motor vehicle (CMV) drivers (if any) in their study population, the generalizability of these findings to CMV drivers is unknown.

Key Question 3: Among individuals who have experienced a TIA, what is the risk of experiencing a future stroke?

A number of conclusions can be drawn from the findings of the analyses described above. These conclusions are presented below:

TIA and Stroke Risk: Overall Findings

Individuals are at an increased risk for stroke following a TIA when compared with their counterparts who did not experience a TIA (Strength of Evidence: Strong).

The increased stroke risk is highest immediately following TIA (within one month) and decreases steadily out to five years following TIA (Strength of Evidence: Moderate).

The entire evidence base of 13 studies (representing approximately 30,000 individuals) consistently reported an elevated risk of stroke in individuals who experienced a TIA compared with controls who did not experience a TIA. Separate analyses based on four moderate-quality cohort studies with data at multiple follow-up periods suggests that the increased risk is very high within the first month following TIA (at least 65 times higher than the risk for individuals

who have not had a TIA) and drops rapidly during the first year. A small cumulative elevated risk continues to decrease steadily out to five years following TIA.

TIA and Stroke Risk: Findings based on Time since TIA

At one month and six months following a TIA event, individuals are at an increased risk for stroke when compared with their counterparts who did not experience a TIA (Strength of Evidence: Moderate).

- **A precise estimate of the magnitude of this increased risk cannot be determined at this time.**

Two studies (Quality Rating: Moderate) at each follow-up time presented data directly relevant to these time points. The data were qualitatively consistent and the magnitude of increased risk at each time point examined was large. Although precise summary effect estimates could not be determined, individuals with TIA had at least a 65-fold increase in risk at one month and a 16-fold increase at six months compared with controls without TIA. Therefore, it is unlikely that future studies will overturn our finding.

At one year following a TIA, individuals are at an increased risk for stroke when compared with their counterparts who did not experience a TIA (Strength of Evidence: Strong).

- **The estimated magnitude of increased risk at one year is RR (risk ratio) = 12.02 (95% CI 5.66 to 25.53) (Stability of Evidence: Low).**

Three studies (Quality Rating: Moderate) presented data at one year following TIA. Pooling of these data revealed that the mean stroke risk associated with TIA is RR = 12.02 (95% CI 5.66 to 25.53) one year after experiencing a TIA, representing a 12-fold increase in risk compared with individuals who have not experienced a TIA. The finding of increased stroke risk was robust, although the stability of the summary effect size was low. The data were qualitatively consistent and the effect size was very large, making it very unlikely that future studies will overturn this finding.

At two and three years following a TIA event, individuals are at an increased risk for stroke when compared with their counterparts who did not experience a TIA (Strength of Evidence: Moderate).

- **A precise estimate of the magnitude of this increased risk cannot be determined at this time.**

Three studies (Quality Rating: Moderate) presented data on stroke risk at three years following TIA. Pooling of these data revealed that the risk of experiencing a stroke three years after a TIA event is at least 1.6 times greater than the control risk level. Two of these studies also evaluated stroke risk at two years, which was found to be elevated by at least three-fold in individuals with TIA compared with controls without TIA.

At four and five years following a TIA event, individuals are at an increased risk for stroke when compared with their counterparts who did not experience a TIA (Strength of Evidence: Minimally Acceptable).

Two studies (Quality Rating: Moderate) at each follow-up time presented data directly relevant to this question. The findings were qualitatively consistent, but the data could not be combined in a pooled analysis. Thus, the evidence is considered minimally acceptable to support the conclusion.

Preface

Organization of Report

This evidence report contains three major sections: 1) *Background*, 2) *Methods*, and 3) *Evidence Synthesis*. These major sections are supplemented by extensive use of appendices.

In the *Background* section, we provide background information about stroke, TIA and driving. Also included in the background section is information on current regulatory standards and guidelines from the FMCSA and three other government transportation safety agencies; the Federal Aviation Administration (FAA), the Federal Railroads Administration (FRA), and the Maritime Administration (MARAD). In addition, we summarize equivalent information from other countries generally considered to have well-developed medical fitness programs. In the *Methods* section, we detail how we identified and analyzed information for this report. The section covers the key questions addressed, details of literature searching, criteria for including studies in our analyses, evaluation of study quality, assessment of the strength of the evidence base for each question, and methods for abstracting and synthesis of clinical study results. The *Evidence Synthesis* section of this report is organized by Key Question. For each question, we report on the quality and quantity of the studies that provided relevant evidence. We then summarize available data extracted from included studies either qualitatively or, when the data permit, qualitatively and quantitatively (using meta-analysis). Each section in the *Evidence Synthesis* section closes with our conclusions, based on our assessment of the available evidence.

Scope

Commercial driving is a hazardous occupation. The trucking industry has the third highest fatality rate of all occupations (12 percent) in the United States. About two thirds of fatally injured truck workers are involved in highway crashes. According to the U.S. Department of Transportation, there were 137,144 non-fatal crashes involving a large truck in 2005. 59,405 of those crashes resulted in an injury to at least one individual, for a total of 89,681 injuries. 4,932 of all crashes caused 5,215 fatalities. In 2006, the U.S. DOT *Brief Statistical Summary* reported a total of 805 motorists killed in large truck crashes, an increase of 0.1 percent over the statistics for 2005 (n = 804). The total number of motorists injured in large truck crashes was 23,000, a decrease of 15 percent when compared with 2005 figures (n = 27,000).(1)

The purpose of this evidence report is to address several key questions posed by the FMCSA. Each of these key questions was carefully formulated by the FMCSA so that its answer will provide information to the FMCSA necessary for the updating its current medical examination guidelines. The key questions addressed in this evidence report are:

Key Question 1: Are individuals who have experienced a stroke at an increased risk for a motor vehicle crash (crash risk or driving performance)?

Key Question 2: If so, can neuropsychological testing of individuals who have experienced a stroke predict crash risk?

Key Question 3: Among individuals who have experienced a TIA, what is the risk of experiencing a future stroke?

Background

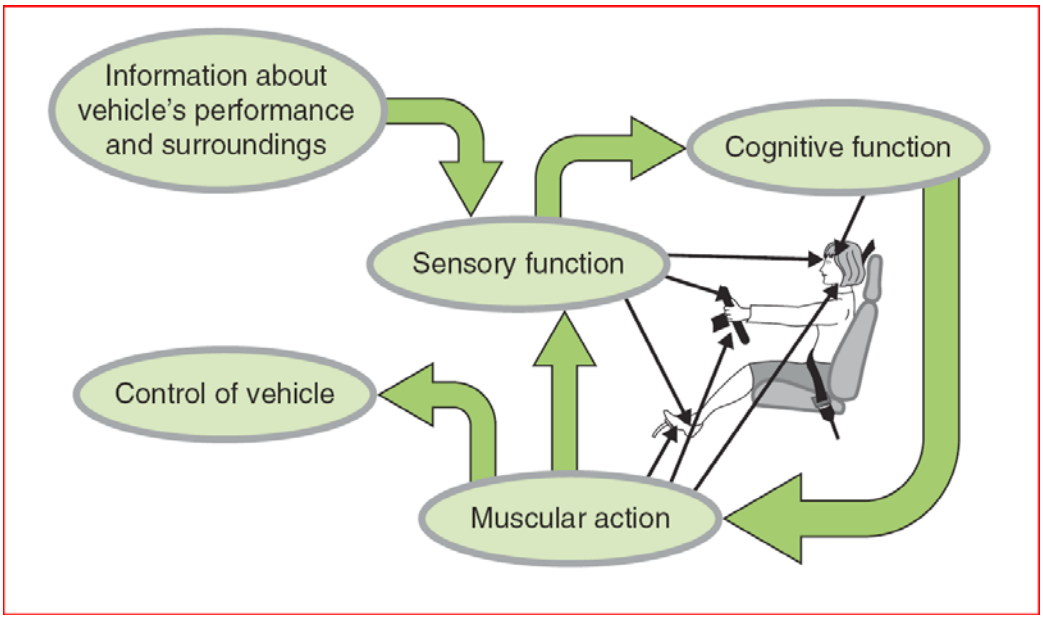
Driving is a complicated psychomotor performance that depends on fine coordination between the sensory and motor systems. It is influenced by factors such as arousal, perception, learning, memory, attention, concentration, emotion, reflex speed, time estimation, auditory and visual functions, decision making and personality. Safe driving requires skills to maintain effective and reliable control of vehicles, the capacity to respond to the road, traffic, and other external clues; and the ability to follow the "rules of the road." Drivers consciously learn all these skills and demonstrate them as part of obtaining their CDL and the vast majority of people have the ability to achieve a satisfactory driving standard.

Driving performance generally improves with experience and eventually becomes an 'over-learned' skill that is subconsciously retained and can readily be used as required. Impairments caused by health problems can interfere with a driver's learned skills and can ultimately affect driving performance (Figure 1) Anything that interferes with any of these factors to a significant degree may impair driving ability. The task of driving can be thought of as a continuous loop, where information about the road, other drivers, and the vehicle is processed by the brain, and this leads to drivers taking action to adjust the speed and direction of the vehicle and to direct their gaze to likely danger areas. The results of these actions then feed back into a further round of adjustments. The loop is dynamic and timing is critical for making continuous adjustments in the light of new perceptions. Within this loop, vision is the dominant sense involved. Visual and other perceptions convey information such as speed, location of vehicles, and other obstacles.

The driver analyzes current perceptions based on prior training and experience about safety risks, vehicle characteristics, and the anticipated behavior of other road users. The intent of the journey in terms of route and destination is also used to decide the actions required, especially at junctions. Current perceptions, learned responses, and intentions about the journey all interact, largely at a subconscious level in an experienced driver. They are converted into musculoskeletal actions so that drivers can adjust the vehicle controls using their hands and feet, and into head and eye movements to direct their gaze. The loop is closed by drivers observing the effects of very recent decisions about the control of the vehicle and adjusting the next ones, while also taking account of new information about the surroundings. Any condition that impairs perception, cognition (including alertness, attitude to risk, and recall) or motor function has the potential to interfere with the whole loop, and thus impair driving and make it less safe. This interference may be constant, as with a defect in vision, or it may be episodic, as in a sudden loss of consciousness. In the long term, the time course and prognosis of the impairing condition, whether fluctuating, progressive, remittent, or a mixed picture, will determine the pattern of future risk.(2)

Cerebrovascular disease refers to any pathological process involving the blood vessels of the brain. It is the most common neurological disorder in adults, and is the third-leading cause of death in the United States, behind heart disease and cancer. Cerebrovascular events such as TIA and stroke have the potential to impair cognitive and motor skills that are required for safe driving. The purpose of this evidence report is to summarize the available data on the relationship between cerebrovascular disorders and CMV driver safety.

Figure 1. The Driving Task



Source: Carter, 2006 (see: http://www.dft.gov.uk/pgr/roadsafety/drs/fitnesstodrive/fitnesstodrive)

I. Definitions, Etiology, and Signs and Symptoms of Transient Ischemic Attack and Stroke

In this section, we provide definitions for various cerebrovasular diseases and describe their etiology and signs and symptoms. Box 1 summarizes the definitions for the cerebrovasular diseases discussed in this report.

Box 1. Definitions of Different Types of Cerebrovascular Disorders

Transient Ischemic Attack (TIA): a brief episode of neurological deficit, having a vascular cause that resolves without any residual effect within 24 hours
Reversible Ischemic Neurological Deficit (RIND): TIAs that last more than 24 hours but resolve in a few days with no permanent deficits
Stroke: a loss of neurological function, caused by vascular injury to the brain that has a sudden onset and lasts over 24 hours
- **Hemorrhagic Stroke:** caused by bleeding in the brain
  - **Intracerebral:** occurs when blood vessels in the brain burst and leak blood in the brain
  - **Subarachnoid:** occurs when blood vessels just outside the brain rupture and leak blood in the brain
- **Ischemic Stroke:** blockage of blood flow in an artery in the head or neck leading to the brain
  - **Thrombotic:** the blockage of cerebral arteries in the brain by the formation of a blood clot; can form in large or small vessels
  - **Embolitic:** blood clots from other parts of the body dislodge and become trapped in arteries closer to the brain

A. Transient Ischemic Attack

Definitions and Eitiology

A TIA is a brief episode of neurological deficit, having a vascular cause that resolves without any residual effect within 24 hours. The length of the episode can vary, but most TIAs resolve within an hour of onset. The term *reversible ischemic neurological deficit (RIND)* has been used to describe these types of episodes that last beyond 24 hours but then resolve within a few days and result in no permanent deficits. Some health care professionals believe that a RIND episode may in fact be an actual stroke that is mild enough to leave no residual deficits.

A TIA begins in the same way that an ischemic stroke does. In ischemic strokes, a clot blocks the blood supply to part of the brain. In a stroke, there is prolonged lack of blood supply that often causes permanent damage to brain tissue. In TIA, a short blockage occurs and it does not seem to leave lasting effects to the brain.(3,4) A person might feel an arm and leg on one side go numb for several hours, then recover. Or s/he may suddenly have trouble seeing, feel dizzy, and lose his or her balance, then feel fine. It is very important to recognize the warning signs of a TIA or stroke, to prevent a recurrent TIA or more severe stroke episode.

The underlying cause of a TIA often is a buildup of cholesterol-containing fatty deposits (atherosclerosis) in an artery or one of its branches that supply oxygen and nutrients to the brain. Plaques can decrease the blood flow through an artery or lead to the development of a clot. Other causes include a blood clot moving to the brain from another part of the body In thrombosis, clots block arteries where they are formed In an embolic event or embolism, clots form, dislodge from their original forming place, move, and get trapped in arteries closer to the brain.(3,4) A special class of embolisms are clots that form in the heart and can travel to the brain. Conditions including a previous heart attack, heart valve abnormalities, a patent foramen ovale, acute heart valve disease and atrial fibrillation, and an irregular and often, rapid heartbeat increase the risk of developing embolisms that develop in the heart and travel to the brain. With these conditions, the heart doesn't pump blood as efficiently, or it beats irregularly, allowing blood clots to form in the chambers of the heart that can break off and travel to the brain.(3,4)

Signs and Symptoms

The signs and symptoms of TIA resemble those found early in someone having a stroke and may include(3-5):

- Sudden tingling, changes in sensation, numbness or paralysis in the face, arm, or leg, typically on one side of the body
- Sudden weakness or heavy feeling of extremities
- Slurred or garbled speech or difficulty understanding others
- Sudden blindness in one or both eyes, double vision, decreased vision, or eye pain

- Dizziness, loss of balance, or loss of coordination
- Difficulty walking and gait changes or staggering
- Falling caused by weakness in the legs
- Confusion and disorientation

Other less frequent signs and symptoms may include(6):

- Apathy or inappropriate behavior
- Excessive somnolence or drowsiness
- Agitation or psychosis
- Inattention to surrounding environment, particularly to one side; if severe, patient may deny deficit or even his or her body parts.

People may have more than one TIA, and the recurrent signs and symptoms may be similar or different depending on which area of the brain is involved.

B. Strokes

Definitions and Eitiology

A cerebrovascular accident (CVA) or stroke is a loss of neurological function, caused by vascular injury to the brain that has a sudden onset and lasts more than 24 hours. With approximately 750,000 strokes and 150,000 stroke deaths each year, stroke ranks as the third leading killer in the United States after heart disease and cancer. Stroke is the leading cause of adult disability in the United States with 2 million of the 3 million Americans who have survived a stroke sustaining some permanent disability. The overall cost of stroke to the nation is approximately $40 billion a year.(7-10)

There are two kinds of stroke—hemorrhagic and ischemic. Hemorrhagic strokes can be intracerebral or subarachnoid, and ischemic strokes can be thrombotic or embolic. Thrombotic strokes can involve large vessel or small vessel thrombosis.(11)

Hemorrhagic strokes are caused by bleeding within the brain (see Figure 2). There are two types of hemorrhagic strokes: intracerebral and subarachnoid. *Intracerebral hemorrhages* occur when blood vessels within the brain burst, leaking blood within the brain. The sudden increase in pressure in the brain can cause damage to the brain cells surrounded by blood. If the amount of blood increases rapidly, the sudden buildup in pressure can lead to unconsciousness or death. Intracerebral hemorrhages usually occur in selected parts of the brain, including the basal ganglia, cerebellum, brainstem, or cortex. The most common cause of intracerebral hemorrhage is hypertension.(11) *Subarachnoid hemorrhages* occur when blood vessels just outside the brain rupture. The subarachnoid space surrounding the brain rapidly fills with blood. Subarachnoid

hemorrhage is most often caused by abnormalities of the arteries at the base of the brain (i.e., arterio-venous malformations) or cerebral aneurysms.(11)

Ischemic strokes are much more common than hemorrhagic strokes. Ischemic strokes are caused by a blockage of blood flow in an artery in the head or neck leading to the brain (see Figure 3). Some ischemic strokes are caused by stenosis or narrowing of arteries because of a build up of plaque, fatty deposits, and blood clots along the artery wall. Atherosclerosis is a vascular disease that can cause stenosis. In atherosclerosis, deposits of plaque build up along the inner wall of large- and medium-sized arteries, decreasing blood flow. Atherosclerosis in the carotid arteries is a major risk factor for ischemic stroke. If the arteries become too narrow, blood cells may collect and form blood clots. These blood clots can block the artery where they are formed (thrombosis), or can dislodge and become trapped in arteries closer to the brain (embolism).(11) (Note: Some sources use the term *thromboembolic event* or *thromboembolism* to refer to the blocking of a blood vessel by a blood clot dislodged from its site of origin.)

Thrombotic strokes occur when diseased or damaged cerebral arteries become blocked by the formation of a blood clot in the brain. When the arteries become too narrow, blood cells may collect and form blood clots. These blood clots can block the artery where they are formed (thrombosis). Clinically referred to as cerebral thrombosis or cerebral infarction, this type of event is responsible for almost 50 percent of all strokes.(11)

Cerebral thrombosis can also be divided into an additional two categories that correlate to the location of the blockage in the brain: large-vessel thrombosis and small-vessel thrombosis. Large-vessel thrombosis is caused when the blockage is in one of the brain's larger blood-supplying arteries, such as the carotid or middle cerebral. Small-vessel thrombosis involves one (or more) of the brain's smaller, yet deeper penetrating arteries and is also called a lacunar stroke.(11)

Embolitic strokes occur when blood clots dislodge and become trapped in arteries closer to the brain (embolism). According to The Internet Stroke Center at Washington University, "an embolic stroke is also caused by a clot within an artery, but in this case the clot (or emboli) was formed somewhere other than in the brain itself. Often from the heart, these emboli will travel the bloodstream until they become lodged and cannot travel any further. This naturally restricts the flow of blood to the brain and results in almost immediate physical and neurological deficits."(11) Atrial fibrillation is the most common cause of emboli. Other causes include heart attacks and abnormatlities of the heart valves.

Although thromboses and emboli are the most common causes of ischemic strokes, there are a few less common causes. These include vasospasm, inflammation, coagulation disorders, drug abuse (particularly cocaine), and traumatic injury to the blood vessels of the neck.(11)

Figure 2. Hemorrhagic Stroke(12)

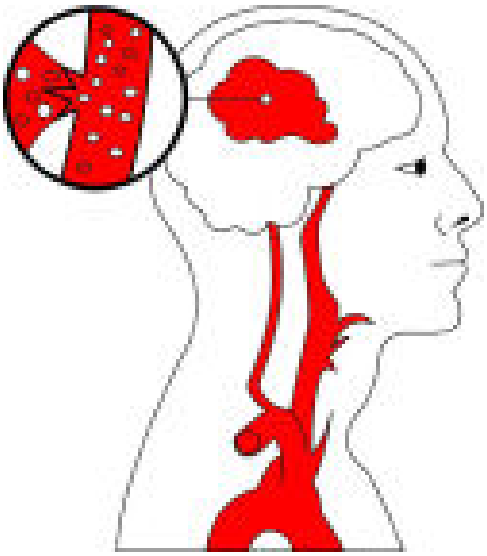
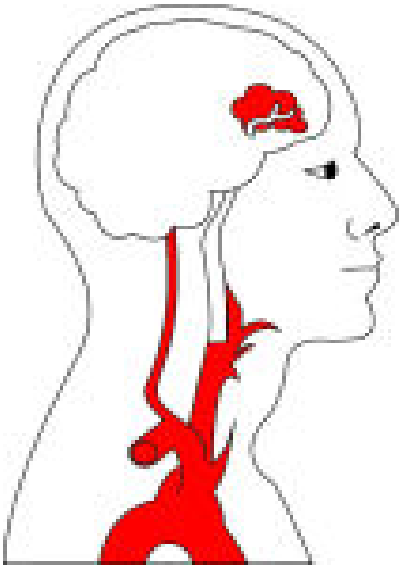


Figure 3. Ischemic Stroke(12)



Signs and Symptoms

The most common sign of stroke is sudden weakness of the face, arm, or leg, most often on one side of the body.(11) Other warning signs can include:

- Sudden numbness or loss of sensation of the face, arm, or leg, especially on one side of the body
- Sudden confusion, trouble speaking, or understanding speech
- Sudden trouble seeing in one or both eyes

- Sudden trouble walking, dizziness, loss of balance or coordination
- Sudden severe headache with no known cause

Symptoms may last a few moments and then disappear. Generally, most people will experience some symptoms as a result of a stroke, but sometimes, they may be symptom free. Since different parts of the brain control different areas and functions, the effects of a stroke generally depend on which part of the brain is injured, and how severely it is injured.(11)

II. Epidemiology of TIA and Stroke

A. Transient Ischemic Attack

Prevalence of TIA

The prevalence of TIA in the United States seems to remain at about 2.3 percent.(13) Based on figures available from the American Heart Association in 2007, the prevalence of TIA in men was estimated at 2.4 percent for ages 65–69, and 3.6 percent for ages 75–79. For women, prevalence was estimated at 1.6% for ages 65-69, and 4.1% for those ages 75–79.(8,14) This is consistent with earlier figures from 1993 where the prevalence of TIA in men was estimated to be 2.7 percent for ages 65–69 and 3.6 percent for ages 75–79, and for women was estimated to be 1.6 percent for ages 65–69 and 4.1 percent for ages 75–79.(9)

In 1999, The National Stroke Association (NSA) sponsored a telephone survey by single-stage random-digit dialing of non-institutionalized U.S. residents ≥ 18 years old. The demographic characteristics of participants were compared with the U.S. population to produce weights for projections. Among 10,112 participants, 2.3 percent reported having been told by a physician that they had a TIA some time in their life. Older age, lower income, and fewer years of education were independently associated with a diagnosis of TIA. An estimated 4.9 million people in the United States report a diagnosis of TIA, and many more recall symptoms consistent with TIA but do not seek medical attention.(13)

Incidence of TIA

From 1998 through 2005, estimates of the annual incidence of TIAs in the United States varied from 200,000 to 500,000.(6,15,16) In population-based studies of the same time period, the age- and gender-adjusted incidence rates for TIA ranged from 68.2 to 83 per 100,000. Males and blacks had higher rates of TIA. A 2000 survey suggested a much higher incidence, with 1 in 15 of those older than age 65 reporting a history of TIA. About 15 percent of patients experiencing stroke reported a history of TIA.http://circ.ahajournals.org/cgi/content/full/115/5/e69 - R11-179730#R11-179730(15,16)

Based on data from the 1993 and 1994 Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), a large U.S. population-based metropolitan study of stroke/TIA incidence rates and outcomes, the population of the study was estimated to be 1.3 million residents, with similar

percentage of blacks and similar socioeconomic demographics to the United States in general.(16) Based on a projection of data from the GCNKSS study, the incidence rate for TIAs in 2002 in the United States was estimated at approximately 240,000 TIA events. This was considered a conservative estimate by the authors. The mean age at the first event was 70.4 years. Blacks comprised 15.2 percent of the patients and other races were 0.4 percent; 53.5 percent were female and 46.5 percent were males; 81.9 percent went to the emergency department; and 78.7 percent of people who went to the emergency department were admitted to the hospital. As indicated in Table 6, the overall annual age- and sex-adjusted incidence rate, adjusted to the 2000 population, for a single TIA during the study period in the population was 83 per 100,000 people.(16)

Blacks had a significantly higher overall incidence of TIA when compared with whites, and men had a significantly higher overall incidence of TIA when compared with women. (See Table 2.) When adjusted for race and gender, the age-adjusted incidence was somewhat higher in black males than white males but not statistically significant. The age-adjusted rate was significantly lower for white females than for all other race and gender groups. (See Table 3.) The highest incidence of TIA of any group was seen in the extremely elderly black men, at 1,558 events per 100,000. The incidence of TIA increased exponentially with age, regardless of race or gender.(16)

Table 2. Incidence Rates of TIA (Per 100 000)(16)

	TIA Incidence Rate*	95% CI
Male	101.4	92.4, 110.4
Female	69.8	64.0, 75.8
Black	98.0	82.1, 113.9
White	81.3	76.0, 86.6
Total	82.9	77.9, 88.0

*Adjusted for age, and race or gender as appropriate, and standardized to the 1990 U.S. population.

Table 3. Age-specific Incidence Rates of TIA Per 100,000 by Race and Gender(16)

Age Range, y	TIA Incidence Rates			
	White Male	White Female	Black Male	Black Female
<35	1.0 (0.0–2.2)	1.8 (0.2–3.3)	1.7 (0.0–5.2)	3.2 (0.0–7.8)
35–44	4.6 (0.1–9.0)	12.3 (5.0–19.6)	16.0 (0.0–38.3)	12.7 (0.0–30.2)
45–54	82.2 (59.2–105.2)	73.3 (52.3–94.2)	129.8 (49.4–210.3)	30.2 (0.0–64.3)
55–64	155.4 (118.7–192.1)	96.3 (69.0–123.5)	205.7 (89.3–322.1)	249.0 (139.9–358.2)
65–74	468.5 (395.7–541.3)	246.6 (201.1–292.1)	338.2 (172.5–503.9)	330.2 (192.2–468.3)
75–84	750.4 (620.9–879.9)	521.1 (441.8–600.4)	612.8 (279.7–945.9)	647.9 (393.9–901.9)
85+	718.5 (457.0–980.0)	589.3 (455.0, 723.5)	1557.9 (478.3–2637.5)	847.8 (346.8, 1348.8)
Overall Adjusted Rates (95% CI)	100.6 (91.1, 110.1)	67.6* (61.4, 73.9)	107.2 (79.8, 134.7)	92.6 (72.9, 112.4)

* White females overall rate less than all others $P < 0.05$.

Data for the prevalence and incidence of TIA in CMV drivers are not available.

B. Strokes

Prevalence of Stroke

The most recent data on the prevalence of strokes in the United States come from the Centers for Disease Control and Prevention 2005 Behavioral Risk Factor Surveillance System (BRFSS). According to CDC and others, stroke is the third most common cause of death in the United States.(9,17) The prevalence of stroke for adults aged 20 years and older in the United States is estimated to be 5,839,000 people or 2.6 percent of the non-institutionalized U.S. population.(9,17) Ischemic stroke is the most common kind of stroke, accounting for 87 to 88 percent of all strokes.(9,11) Ten percent of strokes are intracerebral hemorrhage, and 3 percent of strokes are subarachnoid hemorrhage.(9) Strokes can affect people of all ages, including children. Many people with ischemic strokes are 60 or older, and the risk of stroke increases with age.

As indicated in Table 4, in 2005, CDC noted that significant differences exist in the prevalence of stroke by gender, race/ethnicity, age group, and education level. According to CDC, "The prevalence of stroke increased with age: 8.1 percent of respondents aged ≥65 years reported a history of stroke, compared with 0.8 percent of persons aged 18 to 44 years. The prevalence of stroke among men (2.7 percent) and women (2.5 percent) was similar. Among persons with fewer than 12 years of education, 4.4 percent reported a history of stroke, approximately twice the proportion among college graduates (1.8 percent). The overall prevalence of stroke among American Indians and Alaska Natives (5.8-6.0 percent), multiracial persons (4.6 percent), and blacks (3.4-4.0 percent) were higher than the prevalence among whites (2.3 percent). The prevalence of stroke among Asians/Pacific Islanders (1.6-2.0 percent) and Hispanics (2.2-2.6 percent) were similar to the prevalence among whites (2.3 percent). The prevalence of stroke in American Indian men aged 45 to 74 years ranges from 0.2 percent to 1.4 percent. Among American Indian women in the same age group, the prevalence ranges from 0.2 percent to 0.7 percent."(8,9,17)

Table 4. Prevalence by Age, Gender, Race, and Education, 2005 BRFSS(17)

Characteristic	Total no. of respondents*	Prevalence of Stroke (%)†	(95% CI)	Estimated no. of U.S. residents with a history of stroke
Age group (yrs)				
18-44	128,328	0.8	0.7-0.9	852,000
45-64	137,738	2.7	2.5-2.9	1,926,000
≥65	87,351	8.1	7.7-8.5	3,036,000
Sex¶				
Men	136,201	2.7	2.5-2.8	2,694,000
Women	219,911	2.5	2.4-2.7	3,145,000
Race/Ethnicity¶				
White, non-Hispanic	279,419	2.3	2.3-2.4	4,017,000

Characteristic	Total no. of respondents*	Prevalence of Stroke (%)t	(95% CI)	Estimated no. of U.S. residents with a history of stroke
Black, non-Hispanic	27,925	4.0	3.6-4.5	772,000
Asian/Pacific Islander	5,974	1.6**	1.0-2.7	60,000
Hispanic tt	25,539	2.6	2.1-3.3	616,000
American Indian/Alaska Native	5,535	6.0	4.5-7.8	126,000
Multiracial	6,519	4.6	3.7-5.6	136,000
Education¶				
Less than 12 years	38,202	4.4	4.0-4.9	1,365,000
High school graduate	109,830	2.6	2.5-2.8	1,863,000
Some college	93,228	2.7	2.5-2.9	1,474,000
College graduate	113,944	1.8	1.6-1.9	1,108,000
Total	356,122	2.6	2.5-2.7	5,839,000

* The sums of the smaple sizes in each category might not add up to the total number of respondents because of unknown or missing information
t Weighted percentage of respondents who reported a history of stroke
¶Weighted percentages are age adjusted to the 2000 US standard population
** The relative standard error of this estimate is 20%-30% and should be interpreted with caution
tt Might be of any race

Prevalence by Geographical Region. Researchers have referred to the existence of a "Stroke Belt," traditionally defined as the eight-state region (North Carolina, South Carolina, Georgia, Tennessee, Alabama, Mississippi, Arkansas, and Louisiana) in the Southeast.(18) The Stroke Belt may have stroke mortality approximately 30 percent to 40 percent higher than the rest of the United States.(19) Some researchers estimate that the incidence rate of stokes is approximately 15 percent higher in the Southeast than the rest of the nation.(20)

As indicated in Table 5 and Figure 4, the prevalence of stroke ranged from 1.5 percent in Connecticut to 4.3 percent in Mississippi. States and territories with the highest prevalence of stroke were at approximately twice the level of those with the lowest. Wyoming, with an estimated state population of 509,000 in 2005, had the lowest estimated number of persons reporting a history of stroke (10,000); California, with an estimated population of approximately 36 million in 2005, had the highest (641,000).(7,9,17)

Table 5. Percentage of Adults in the United States with a History of Strokes By State(17)

State/Area	Total no. of respondents	Weighted, age-adjusted prevalence of stroke (%)*	(95% CI)	Estimated no. of residents with a history of stroke t
Alabama	3.197	3.2	2.7-3.9	117,000
Alaska	2,813	2.5	1.7-3.5	8,000
Arizona	4,710	2.1	1.6-2.6	88,000
Arkansas	5,280	3.0	2.5-3.4	63,000
California	6,134	2.6	2.1-3.2	641,000
Colorado	5,979	1.7	1.4-2.0	49,000

State/Area	Total no. of respondents	Weighted, age-adjusted prevalence of stroke (%)*	(95% CI)	Estimated no. of residents with a history of stroke †
Connecticut	5,254	1.5	1.2-1.9	45,000
Delaware	4,192	2.6	2.1-3.3	17,000
District of Columbia	3,743	3.4	2.7-4.2	14,000
Florida	8,190	2.8	2.4-3.3	432,000
Georgia	6,064	2.9	2.4-3.4	164,000
Hawaii	6,416	2.8	2.3-3.4	28,000
Idaho	5,734	2.4	2.0-2.9	24,000
Illinois	5,077	3.0	2.3-3.8	278,000
Indiana	5,635	2.5	2.1-3.0	119,000
Iowa	5,051	2.6	2.2-3.1	67,000
Kansas	8,626	2.3	2.0-2.6	49,000
Kentucky	6,628	3.1	2.7-3.7	102,000
Louisiana	2,936	3.3	2.6-4.0	91,000
Maine	3,960	2.4	2.0-2.9	27,000
Maryland	8,632	2.1	1.8-2.5	89,000
Massachusetts	8,906	2.1	1.8-2.6	111,000
Michigan	12,136	3.0	2.6-3.3	225,000
Minnesota	2,829	1.7	1.3-2.2	65,000
Mississippi	4,439	4.3	3.6-5.0	91,000
Missouri	5,164	3.1	2.7-3.7	147,000
Montana	4,983	2.1	1.7-2.5	16,000
Nebraska	8,332	2.2	1.9-2.6	31,000
Nevada	3,161	3.2	2.3-4.4	51,000
New Hampshire	6,038	2.6	2.2-3.1	26,000
New Jersey	13,663	2.1	1.8-2.4	146,000
New Mexico	5,585	2.2	1.8-2.6	31,000
New York	7,796	2.4	1.9-3.0	365,000
North Carolina	17,261	2.8	2.5-3.0	179,000
North Dakota	4,010	1.8	1.5-2.2	10,000
Ohio	7,498	2.3	1.9-2.7	207,000
Oklahoma	13,707	3.4	3.0-3.8	95,000
Oregon	12,015	2.5	2.2-2.8	72,000
Pennsylvania	13,378	2.2	1.9-2.5	237,000
Rhode Island	3,976	2.1	1.7-2.6	19,000
South Carolina	8,440	2.9	2.6-3.3	96,000
South Dakota	6,915	2.6	2.2-3.0	16,000
Tennessee	4,749	3.1	2.6-3.7	142,000

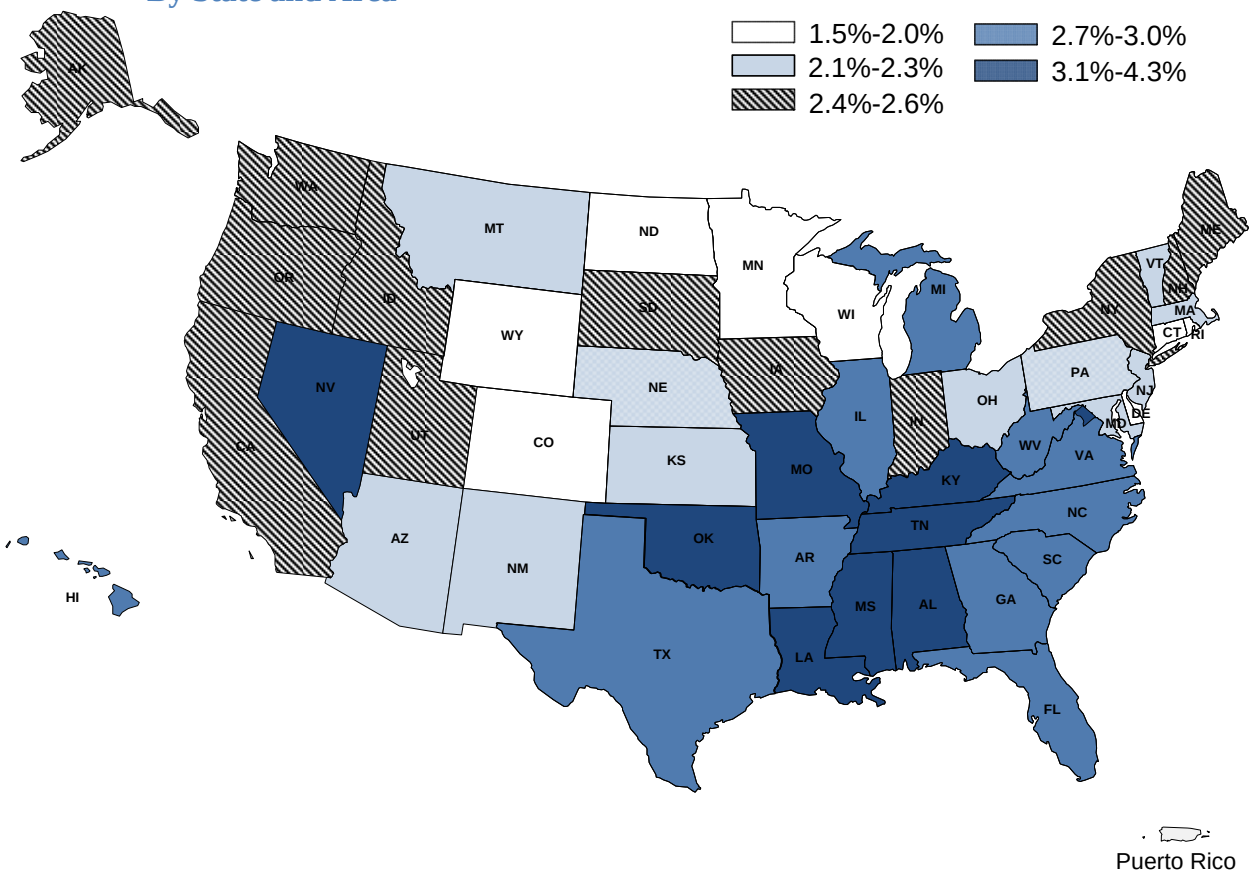
State/Area	Total no. of respondents	Weighted, age-adjusted prevalence of stroke (%)*	(95% CI)	Estimated no. of residents with a history of stroke †
Texas	6,512	3.0	2.6-3.4	455,000
Utah	5,137	2.6	2.1-3.1	34,000
Vermont	6,763	2.1	1.8-2.5	11,000
Virginia	5,493	2.7	2.2-3.2	146,000
Washington	23,302	2.4	2.2-2.6	108,000
West Virginia	3,553	3.0	2.5-3.6	48,000
Wisconsin	4,900	1.9	1.5-2.4	81,000
Wyoming	5,009	1.9	1.5-2.3	7,000
Puerto Rico	3,789	1.9	1.5-2.4	54,000
US Virgin Islands	2,422	--¶	---	---
Total	356,112	2.6	2.5-2.7	5,839,000

*Weighted percentages are age standardized to the 2000 US standard population

**Estimated number of persons in each state/area with a history of stroke (rounded to the nearest thousand), based on 2000 US standard population

¶Data omitted because they have a relative standard error >30% or a numerator of <50 respondents

Figure 4. 2005 BRFSS: Percentage of Adults in the United States with a History of Stroke By State and Area



Based on the results of CDC's 2003 BRFSS, African Americans and others residing in the southeastern United States seem to be disproportionately affected by stroke. 2003 BRFSS findings indicate a 1.23 percent higher prevalence of stroke in 10 southeastern states (Alabama, Arkansas, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, and Virginia) than in 13 non-southeastern states (Alaska, Colorado, Connecticut, Hawaii, Maine, Maryland, Minnesota, Montana, Nebraska, New York, North Dakota, Ohio, and West Virginia) and DC. The highest age-adjusted prevalence of stroke was found among southeastern African Americans, followed by non-southeastern African Americans, southeastern whites, and non-southeastern whites.(8,21)

As indicated in Table 6 and Table 7, the greater proportion of blacks in the southeastern states seems to have accounted for some of the higher prevalence in the southern states. However, differences in education level and prevalence of risk factors such as diabetes and high blood pressure accounted for approximately half of the difference in stroke prevalence between southeasterners and non-southeasterners and approximately three fourths of the difference in prevalence between blacks and whites. Perhaps these findings reinforce the importance of primary and secondary prevention of known risk factors (e.g., diabetes, high blood pressure, and smoking) for stroke.(8,21)

Table 6. Stroke Prevalence by Age, Gender, Education, and Risk Factors(21,22)

Characteristics	Southeastern states*		Nonsoutheastern states** and DC	
	Black % (95% CI)	White % (95% CI)	Black % (95% CI)	White % (95% CI)
Age group (yrs)				
18-34	38.9 (37.4-40.4)	28.5 (27.8-29.2)	31.1 (28.4-33.9)	27.8 (27.0-28.6)
35-44	21.2 (20.0-22.3)	20.1 (19.6-20.7)	23.6 (21.3-26.1)	20.2 (19.6-20.9)
45-54	17.8 (16.8-18.8)	18.9 (18.3-19.4)	19.3 (17.2-21.7)	19.3 (18.7-19.9)
55-64	10.5 (9.8-11.3)	14.8 (14.3-15.2)	12.6 (10.8-14.7)	14.3 (13.8-14.8)
≥65	11.6 (10.9-12.4)	17.7 (17.3-18.2)	13.3 (11.3-15.6)	18.4 (17.8-18.9)
Sex				
Men	44.4 (42.9-45.9)	48.8 (47.6-49.0)	43.8 (40.9-46.8)	48.1 (47.3-48.9)
Women	55.6 (54.1-57.1)	51.7 (51.0-52.4)	56.2 (53.2-59.1)	51.9 (51.1-52.7)
Education level				
Less than high school graduate	18.9 (17.9-20.0)	11.8 (11.4-12.2)	13.3 (11.2-15.7)	8.1 (7.6-8.6)
High school graduate	36.9 (35.5-38.4)	31.4 (30.8-32.0)	35.9 (33.1-38.8)	30.3 (29.6-31.1)
Some college	26.0 (24.7-27.3)	27.3 (26.7-27.9)	25.4 (23.0-27.9)	25.9 (25.2-26.6)
College graduate	18.2 (17.1-19.3)	29.5 (28.9-30.1)	25.4 (23.1-27.9)	35.7 (34.9-36.4)
Has diabetes	12.1 (11.2-12.9)	7.6 (7.2-7.9)	10.7 (9.1-12.6)	6.8 (6.4-7.2)
Has high blood pressure	33.8 (32.5-35.1)	28.3(27.7-28.8)	30.0 (27.5-32.8)	24.9 (24.3-25.6)
Smoking Status¶				
Never smoked	63.4 (62.0-64.8)	49.4 (48.7-50.1)	59.7 (56.8-62.5)	49.9 (49.1-50.6)

Characteristics	Southeastern states*		Nonsoutheastern states** and DC	
	Black % (95% CI)	White % (95% CI)	Black % (95% CI)	White % (95% CI)
Formerly smoked	14.1 (13.2-15.1)	25.0 (24.5-25.6)	17.0 (15.0-19.3)	28.2 (27.5-28.9)
Currently smokes	22.5 (21.3-23.8)	25.5 (24.9-26.2)	23.3 (21.0-25.8)	22.0 (21.3-22.7)
Has health-care coverage	77.4 (76.1-78.6)	86.4 (85.9-86.9)	83.9 (81.7-86.0)	89.2 (88.7-89.8)

*Alabama, Arkansas, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, and Virginia
**Alaska, Colorado, Connecticut, Hawaii, Maine, Maryland, Minnesota, Montana, Nebraska, New York, North Dakota, Ohio, and West Virginia
¶Categorized as follows: never smoked (fewer than 100 cigarettes in lifetime), formerly smoked (at least 100 cigarettes in lifetime but not currently smoking), or currently smokes (smoked at least 100 cigarettes in lifetime and currently smokes every day or some days)

Table 7. Stroke Prevalence by Region(8,21)

Adjustments	Southeastern states* versus nonsoutheastern states¶ and DC		Blacks versus Whites	
	Adjusted Odds Ratio	95% CI	Adjusted Odds Ratio	(95% CI)
Age- and sex-adjusted	1.43	1.26-1.61	1.61	1.37-1.88
Age-, sex-, and race-adjusted	1.37	1.21-1.55	---	---
Age-, sex-, and region-adjusted	---	---	1.52	1.29-1.78
Fully adjusted model **	1.23	1.08-1.40	1.13	0.96-1.33

*Alabama, Arkansas, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, and Virginia
¶Alaska, Colorado, Connecticut, Hawaii, Maine, Maryland, Minnesota, Montana, Nebraska, New York, North Dakota, Ohio, and West Virginia
**In addition to adjusting for age, sex, and race or region, the fully adjusted model was adjusted for education level, having diabetes, having high blood pressure, smoking status, and having a health-care plan

Incidence of Stroke

The American Heart Association incidence estimates for various types of cardiovascular disease are extrapolations to the U.S. population from the Framingham Heart Study (FHS), the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS) conducted by the NHLBI, and the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) funded by the National Institute of Neurological Disorders and Stroke (NINDS). The rates change only when new data are available; they are not computed annually, and they are not comparable with past issues of the Heart and Stroke Statistical Update (renamed Heart Disease and Stroke Statistics Update).(8)

Each year about 780,000 people experience a new or recurrent stroke. About 600,000 of these are first attacks, and 200,000 are recurrent attacks (GCNKSS, FHS, ARIC, NHLBI). On average, someone in the United States has a stroke every 40 seconds.

Gender. Each year, about 60,000 more women than men have a stroke (GCNKSS). As is the case with prevalence rates, men's stroke incidence rates are greater than women's at younger ages but not at older ages. The male/female incidence was 1.25 in those 55 to 64 years of age, 1.50 in

those 65 to 74 years of age, 1.07 in those 75 to 84 years of age, and 0.76 in those ≥85 years of age (ARIC and CHS studies).(7-9)

Ethnicity. Blacks have a risk of first-ever stroke that is almost twice that of whites. The age-adjusted stroke incidence rates in those 45 to 84 years of age are 6.6 per 1000 population in black males, 3.6 in white males, 4.9 in black females, and 2.3 in white females (ARIC).(7-9) On the basis of 1987–2001 data from the ARIC study of the NHLBI, stroke/TIA incidence rates (per 1,000 person-years) are 2.4 for white males 45 to 54 years of age, 6.1 for white males 55 to 64 years of age, and 12.2 for white males 65 to 74 years of age. For white women in the same age groups, the rates are 2.4, 4.8, and 9.8 respectively. For black men in the same age groups, the rates are 9.7, 13.1, and 16.2, and for black women the rates are 7.2, 10.0, and 15.0, respectively. As indicated in Figure 5 and Figure 6, black males seem to have the highest incidence of first cerebral infarction and of first intracerebral hemorrhage, especially as age increases.(8)

The Brain Attack Surveillance in Corpus Christi project (BASIC) demonstrated an increased incidence of stroke among Mexican Americans compared with non-Hispanic whites in this community. The crude cumulative incidence was 168/10,000 in Mexican Americans and 136/10,000 in non-Hispanic whites. Specifically, Mexican Americans have an increased incidence of intracerebral hemorrhage and subarachnoid hemorrhage as compared with non-Hispanic whites, adjusted for age, as well as an increased incidence of ischemic stroke and TIA at younger ages compared with non-Hispanic whites.(8,9)

From 1969 through 1988, the age-adjusted annual incidence rate (per 1,000) for total stroke in Japanese-American men has declined markedly from 5.1 to 2.4; for thromboembolic stroke, from 3.5 to 1.9; and for hemorrhagic stroke, from 1.1 to 0.6. The estimated average annual declines are 5 percent for total stroke, 3.5 percent for thromboembolic stroke, and 4.3 percent for hemorrhagic stroke. The decline in stroke mortality in the Honolulu Heart Program (HHP) target population was similar to that reported for U.S. white males 60 to 69 years of age during the same period (the 1969–1988 follow-up period of the HHP) (NHLBI).(8)

Among American Indians 65 to 74 years of age, the annual rates per 1,000 population of new and recurrent strokes are 6.1 for men and 6.6 for women (Strong Heart Study [SHS] 1989–2002; NHLBI).(8)

According to data from the Northern Manhattan Study (NOMAS), the age-adjusted incidence of first ischemic stroke per 100,000 was 88 in whites, 191 in blacks, and 149 in Hispanics. Among blacks, as compared with whites, the relative rate of intracranial atherosclerotic stroke was 5.85; extracranial atherosclerotic stroke, 3.18; lacunar stroke, 3.09; and cardioembolic stroke, 1.58. Among Hispanics compared with whites, the relative rate of intracranial atherosclerotic stroke was 5.00; extracranial atherosclerotic stroke, 1.71; lacunar stroke, 2.32; and cardioembolic stroke, 1.42.(8)

Data for the prevalence and incidence of stroke in CMV drivers were not available.

Figure 5. Annual Rate of First Cerebral Infarction by Age, Sex, and Race (GCNKSS: 1993–1994)(8)

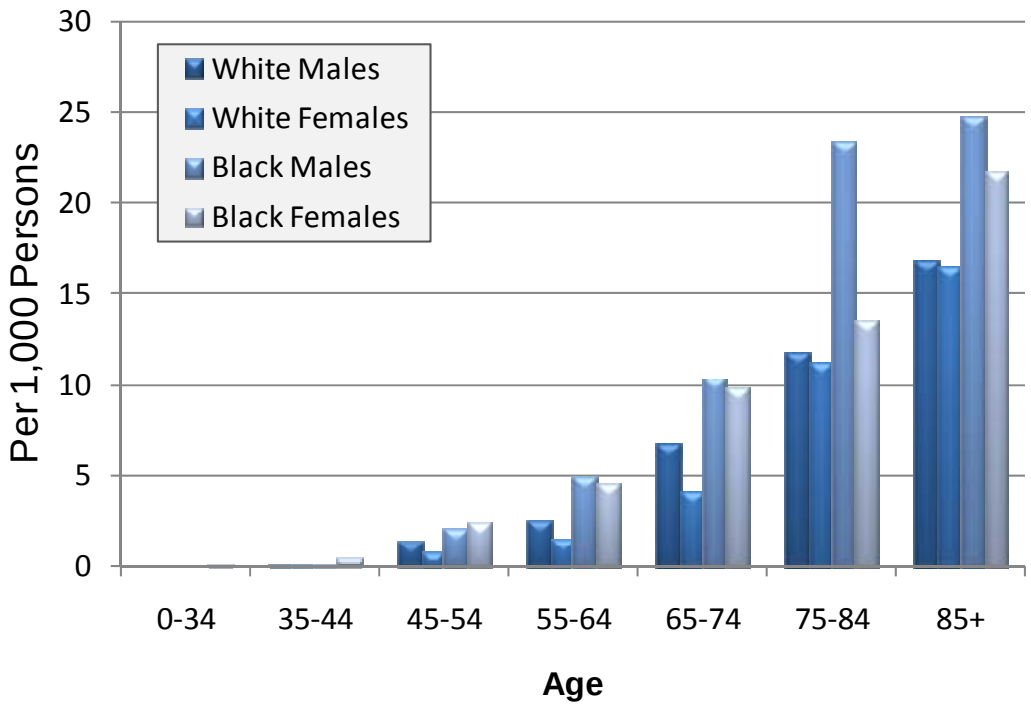
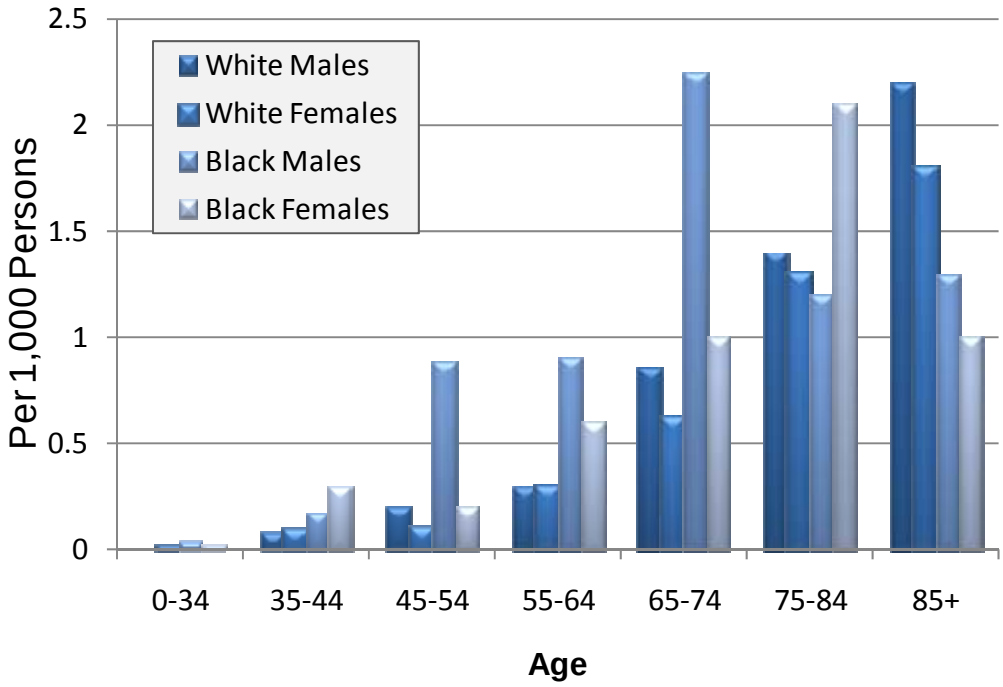


Figure 6. Annual Rate of First Intracerebral Hemorrhage by Age, Sex, and Race (GCNKSS: 1993–1994)(8)



Silent Stroke / Silent Cerebral Infarction. Some researchers have noted that the current estimates of stroke incidence and prevalence in the United States may actually underestimate the nation's stroke burden because they generally do not take into account the occurence of silent infarcts and hemorrhages.(23) Silent strokes or cerebral infarctions include episodes when blood flow to the brain is compromised, resulting in damage, but there with no apparent symptoms. . . . . Below are some estimates of the incidence and prevalence of cerebrovascular disease when asymptomatic episodes are taken into account.

"Estimated age-specific annual incidence rates (per 100,000) of persons experiencing first silent MRI infarct ranged from 1,600 in the age 30–39 stratum to 16,400 at ages 75–79. Estimated incidence rates of first silent MRI cerebral hemorrhage ranged from 180 in ages 30–39 to 6,900 at age >85. Overall, the projected annual incidence in 1998 of U.S. individuals experiencing first silent MRI infarct was 9,040,000, and first silent MRI hemorrhage 1,940,000. Conclusions: In 1998, more than 11 million persons experienced stroke in the U.S., in whom approximately 770,000 were symptomatic and 11 million were first-ever silent MRI infarcts or hemorrhages. These findings demonstrate the incidence of stroke is substantially higher than suggested by estimates based solely on clinically manifest events."(23)

The prevalence of silent cerebral infarction from age 55 through 64 years is about 11 percent. This prevalence increases to 22 percent from ages 65 through 69, 28 percent from ages 70 through 74, 32percent from ages 75 through 79, 40 percent from ages 80 through 85, and 43 percent above age 85. Applying these rates to 1998 U.S. population estimates results in an estimated 13 million people with prevalent silent stroke.(8)

Survival Data

The median survival times (in years) after a first stroke are:

- At 60 through 69 years of age: 6.8 for men and 7.4 for women.
- At 70 through 79 years of age: 5.4 for men and 6.4 for women.
- At ≥80 years of age: 1.8 for men and 3.1 for women.

Mortality Data

On the basis of pooled data from the NHLBI(7):

The one-year mortality rates after a first stroke were:

- At ≥40 years of age, 21 percent of men and 24 percent of women.
- At 40 to 69 years of age: 14 percent of white men, 20 percent of white women, 19 percent of black men, and 19 percent of black women.
- At ≥70 years of age: 24 percent of white men, 27 percent of white women, 25 percent of black men, and 22 percent of black women.

The five-year mortality rates after a first stroke were:

- At ≥40 years of age: 47 percent of men and 51 percent of women.
- At 40 to 69 years of age: 32 percent of white men, 32 percent of white women, 34 percent of black men, and 42 percent of black women.
- At ≥70 years of age: 58 percent of white men, 58 percent of white women, 49 percent of black men, and 54 percent of black women.

The following list of "facts" has been taken from the American Heart Association's Heart Disease and Stroke Statistics—2008 Update.(7) Mortality here refers to the number of deaths for which stroke is considered the underlying cause.(24,25) Mortality facts follow:

- Stroke mortality was 150,074 in 2004.(25)
- Stroke accounted for approximately 1 of every 16 deaths in the United States in 2004.(25)
- Approximately 54 percent of stroke deaths in 2004 occurred out of the hospital.(25)
- When considered separately from other cardiovascular diseases (CVDs), stroke ranked third among all causes of death, behind diseases of the heart and cancer.(24)
- On average, every 3 to 4 minutes, someone dies of a stroke.(22,24)
- Among persons 45 to 64 years of age, 8 percent to 12 percent of ischemic strokes and 37 percent to 38 percent of hemorrhagic strokes result in death within 30 days, according to the ARIC study of the National Heart, Lung, and Blood Institute.(26)
- In a study of persons ≥65 years of age recruited from a random sample of Health Care Financing Administration Medicare Part B eligibility lists in four U.S. communities, the one-month case fatality rate was 12.6 percent for all strokes, 8.1 percent for ischemic strokes, and 44.6 percent for hemorrhagic strokes.(27)
- From 1994 through 2004, the stroke death rate fell 24.2 percent, and the actual number of stroke deaths declined 6.8 percent.(24)
- Conclusions about changes in stroke death rates from 1983 to 2004 are: a) There was a greater decline in stroke death rates in males than in females, with a male–female ratio decreasing from 1.11 to 1.03 (age-adjusted), b) There were greater declines in stroke death rates at ≥65 years of age in men than in women compared with younger ages.(24)
- The 2004 overall death rate for stroke was 50.0 per 100,000. Death rates were 48.1 for white males, 74.9 for black males, 47.2 for white females, and 65.5 for black females.(24)

- In 2004, death rates for stroke were 41.5 for Hispanic or Latino males and 35.4 for females; 44.2 for Asian or Pacific Islander males and 38.9 for females; and 35.0 for American Indian/Alaska Native males and 35.1 for females.(28)
- Because women live longer than men, more women than men die of stroke each year. Women accounted for 61.0 percent of U.S. stroke deaths in 2004.(7)
- From 1995 through 1998, age-standardized mortality rates for ischemic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage were higher among blacks than whites. Death rates from intracerebral hemorrhage were also higher among Asians/Pacific Islanders than among whites. All minority populations had higher death rates from subarachnoid hemorrhage than did whites. Among adults 25 through 44 years of age, blacks and American Indians/Alaska Natives had higher risk ratios than did whites for all three stroke subtypes.(29)
- In 2002, death certificate data showed that the mean age at stroke death was 79.6 years; however, males had a younger mean age at stroke death than females. Blacks, American Indians/Alaska Natives, and Asians/Pacific Islanders had younger mean ages than whites, and the mean age at stroke death was also younger among Hispanics than non-Hispanics.(30)
- Age-adjusted stroke mortality rates began to level in the 1980s and stabilized in the 1990s for both men and women, according to the Minnesota Heart Study. Women had lower rates of stroke mortality than men did throughout the period. Some of the improvement in stroke mortality may be the result of improved acute stroke care, but most is thought to be the result of improved detection and treatment of hypertension.(31)

As is indicated in Table 4, during 2004, the states of Alaska, Arkansas, South Carolina, North Carolina, Oklahoma, and Tennessee had the highest death rates from stroke (60 and older) and the states of New York, Connecticut, Washington DC, New Jersey, and Rhode Island had the lowest death rates for stroke (in the 30s). The overall death rate in 2004 in the United States caused by stroke was 51 per 100,000, and the overall decrease in deaths due to strokes from 1994 to 2004 was 24.2 percent.(7)

Table 8. 2004 Age-Adjusted Death Rates for Stroke by State (Includes District of Columbia and Puerto Rico)(32)

State	Rank	Death Rate	% Change‖ 1994 to 2004
Alabama	50	64.8	-5.7
Alaska	30	51.4	-29.2
Arizona	10	43.3	-26.4
Arkansas	52	65.1	-24.3
California	32	52.8	-21.3
Colorado	14	44.2	-21.1

State	Rank	Death Rate	% Change‖ 1994 to 2004
Connecticut	2	37.8	-28.8
Delaware	6	40.5	-20.4
District of Columbia	4	38.8	-46.8
Florida	8	41.9	-24.8
Georgia	46	59.8	-21.7
Hawaii	18	47.3	-19.1
Idaho	35	53.9	-19.8
Illinois	26	50.1	-26.4
Indiana	36	53.9	-29.0
Iowa	24	49.4	-20.7
Kansas	31	51.5	-19.0
Kentucky	42	58.0	-19.2
Louisiana	44	59.3	-17.5
Maine	27	50.8	-14.3
Maryland	29	51.3	-21.1
Massachusetts	9	42.6	-19.5
Michigan	25	50.0	-28.2
Minnesota	16	46.2	-34.5
Mississippi	45	59.7	-16.8
Missouri	40	55.8	-19.9
Montana	15	45.6	-27.8
Nebraska	20	47.8	-22.7
Nevada	34	53.6	-17.2
New Hampshire	12	43.7	-34.0
New Jersey	5	39.3	-29.7
New Mexico	7	40.6	-32.4
New York	1	32.7	-31.8
North Carolina	48	60.9	-27.5
North Dakota	37	54.3	-23.5
Ohio	28	51.1	-17.4
Oklahoma	47	60.4	-10.9
Oregon	43	58.1	-25.7
Pennsylvania	19	47.3	-24.2
Puerto Rico¶	22	48.2	-17.6
Rhode Island	3	38.4	-30.2
South Carolina	51	64.9	-28.4
South Dakota	21	47.8	-24.2
Tennessee	49	64.5	-24.8
Texas	41	56.3	-19.0

State	Rank	Death Rate	% Change‖ 1994 to 2004
Utah	17	46.9	-21.1
Vermont	11	43.6	-32.6
Virginia	39	55.2	-24.7
Washington	33	53.4	-21.3
West Virginia	38	54.4	-12.7
Wisconsin	23	48.9	-29.6
Wyoming	13	43.9	-30.5
Total United States		51.1	-24.2

As indicated in Table 9, the United States has one of the lowest death rates caused by strokes for both men and women. The Russian Federation, Bulgaria, and Romania have the highest death rates caused by strokes. Death rates are not all taken from the same year.

Table 9. International Death Rates (Revised 2007): Death Rates (Per 100,000 People) for Stroke in Selected Countries (Most Recent Year Available)(7)

Population	Stroke Death Rate (Deaths/100,000)
Men, Ages 35–74 y	
Russian Federation (2002)	453
Bulgaria (2004)*	227
Romania (2004)	251
Hungary (2003)	181
Poland (2003)	118
Czech Republic (2004)	94
China Rural (1999)*	243
Argentina (2001)	103
China Urban (1999)*	217
Scotland (2002)	61
Ireland (2002)	41
Finland (2004)	54
Colombia (1999)	95
Northern Ireland (2002)	53
Greece (2003)*	68
England/Wales (2002)	49
Belgium (1997)*	50
United States (2004)	**35**
Denmark (2001)	52
New Zealand (2000)	40
Germany (2004)	39
Portugal (2003)	96
Sweden (2002)	44

Population	Stroke Death Rate (Deaths/100,000)
Republic of Korea (2002)	143
Mexico (2001)	58
Austria (2004)	34
The Netherlands (2004)	37
Italy (2002)*	41
Norway (2003)	36
Canada (2002)	28
Spain (2003)	43
Australia (2002)	30
France (2002)	35
Switzerland (2002)	23
Israel (2003)	38
Japan (2003)	66
Women Ages 35–74	
Russian Federation (2002)	257
Bulgaria (2004)*	133
Romania (2004)	166
Hungary (2003)	91
China Rural (1999)*	152
China Urban (1999)*	147
Colombia (1999)	71
Poland (2003)	63
Czech Republic (2004)	52
Scotland (2002)	48
Argentina (2001)	55
Mexico (2001)	47
Northern Ireland (2002)	41
United States (2004)	**27**
England/Wales (2002)	36
New Zealand (2000)	33

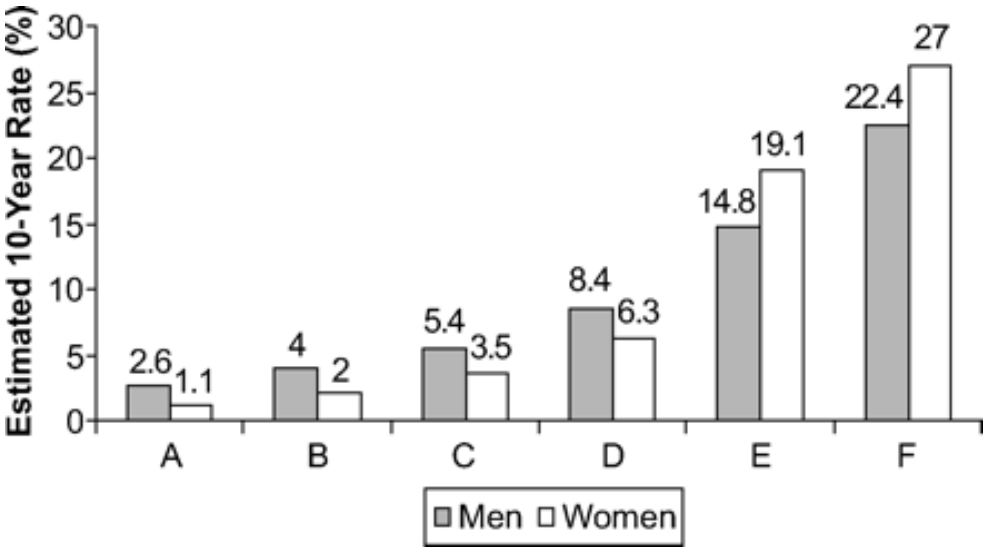
III. Risk Factors for Cerebrovascular Disease

There are numerous factors that can increase or decrease an individual's risk of developing cerebrovascular disease. Some of these are modifiable while others cannot be changed. This section provides a brief overview of the major risk factors and protective factors for cerebrovascular disease.

A. Unmodifiable Risk Factors:

- **Racial/Ethnic Risk Factors.** African Americans have twice the risk for stroke than Caucasians have. Hispanics and Asian/Pacific Islanders have a higher risk for stroke than Caucasians. According to CDC(17), differences in stroke prevalence observed among racial/ethnic groups may be attributed, in part, to differences in the proportion of these population groups with risk factors for stroke. For example, African American men have been found to have a higher prevalence of hypertension and hypercholesterolemia than any other racial/ethnic group, and African American men and women seem to have the highest prevalence of obesity, current smoking, and diabetes.(17,33) Similarly, African Americans have a much higher prevalence of hypertension and diabetes and are less likely to have blood pressure controlled or diabetes treated than whites (12,47).(8,17) Based on a 1989 Atherosclerosis Risk in Communities Study (ARIC)(34), researchers found that African Americans had a three-fold higher multivariate-adjusted risk ratio of lacunar stroke compared with whites, while no difference in nonlacunar strokes was found after adjusting for prevalent risk factors between these two groups.(17) More research is needed to investigate race and ethnic risks of stroke.
- **Heredity.** A person's risk of having a TIA or stroke is greater if a parent, grandparent, sister, or brother has had a stroke.(7-9,11,12,35)
- **Age.** A stroke can happen to anyone, but the risk of stroke increases with age. After the age of 55, the stroke risk doubles for every decade. In adults over 55 years of age, the lifetime risk for stroke is greater than 1 in 6. Many agree that the older people get, the more likely they are to develop heart disease or have a stroke.(7-9,11,12,35)
- **Gender.** Stroke is more common in men than women. But more women than men die from stroke. Women account for more than half of all stroke deaths. Women who are pregnant, take birth control pills and smoke, or have high blood pressure or other risk factors, have a higher stroke risk.(35) As indicated in Figure 6, men have a higher 10-year risk of stroke at younger ages where as women have a higher risk of stroke than men at older ages.(8,36)

Figure 7. Estimated 10-year Stroke Risk in 55-year-old Adults by Gender(8,36)



B. Modifiable Risk Factors:

Diabetes. Diabetes most often appears in middle age and among overweight people. It affects many more women than men after age 60. Compared with women without diabetes, women with diabetes have two to four times the risk of heart disease.(35) While diabetes is treatable, having it still increases a person's risk of heart disease and stroke. Diabetes increases the severity of atherosclerosis—narrowing of the arteries caused by accumulation of fatty deposits—and increasing the speed with which it develops.(3,4) Many people with diabetes also have high blood pressure and high blood cholesterol. These increase their risk for stroke.(7-9,11,12,35)

According to data from the GCNKSS study(37), ischemic stroke patients with diabetes are younger, more likely to be African American, and more likely to have hypertension, myocardial infarction (MI), and high cholesterol than are non-diabetic patients. Age-specific incidence rates and rate ratios show that diabetes increases ischemic stroke incidence at all ages, but this risk is most prominent before age 55 in African Americans and before age 65 in whites. One-year case fatality rates after ischemic stroke were not different between those patients with and without diabetes.

- **High Cholesterol**. High blood levels of low-density lipoprotein (LDL) cholesterol and triglycerides, or low levels of high-density lipoprotein (HDL) cholesterol increase the risk of narrowed or blocked arteries.(3,4) Having a high cholesterol level can lead to a build up of cholesterol and other substances in the inner walls of arteries. This buildup of plaque can narrow the arteries and reduce blood flow. Plaques that rupture can cause blood clots that can totally block blood flow in the artery (thrombosis). Also, clots can break off and travel to another part of the body (embolism). If a clot blocks an artery that feeds the heart, it causes a heart attack. If it blocks an artery that feeds the brain, it causes

a stroke. (Note: Some sources use the term *thromboembolic event* to refer to the blocking of a blood vessel by a blood clot dislodged from its site of origin.)

Results from the Honolulu Heart Program (HHP)(38) indicated that in elderly Japanese men 71 through 93 years of age, low concentrations of high-density lipoprotein (HDL) cholesterol were more likely to be associated with a future risk of thromboembolic stroke than were high concentrations.(38) The reverse seems to be true for LDL. People can lower their LDL by eating a diet low in saturated fat, trans fat, and cholesterol, and engaging in an exercise plan. A doctor may also prescribe cholesterol-lowering drugs, especially if a change in diet and an increase in exercise do not decrease LDL. Even if there is a need to take cholesterol-lowering drugs, a healthy diet and exercise are still important.(7-9,11,12,35)

- **High Blood Pressure/Hypertension.** Having high blood pressure, 140/90 millimeters of mercury or higher, increases the risk of TIA or stroke. High blood pressure (BP) makes the heart work harder than normal. This makes both the heart and arteries more prone to injury. High blood pressure raises the risk of heart attacks, strokes, kidney failure, eye damage, congestive heart failure, and atherosclerosis.(7-9,11,12,35) According to AHA(8), people with BP less than 120/80 mm Hg have about half the lifetime risk of stroke of subjects with hypertension.(37)

- **Smoking.** Smoking is the single most preventable cause of death in the United States. It is associated with a higher risk of illness and death from heart attack, stroke, and other diseases, such as lung, mouth and throat cancers; chronic lung diseases and infections; congestive heart failure; and peripheral vascular disease (in the legs and arms).(7-9,11,12,35) Constant exposure to other people's tobacco smoke increases the risks, even if the person does not smoke. When a person stops smoking, his or her risk of heart disease and stroke starts to drop. Smoking contributes to development of cholesterol-containing fatty deposits in arteries (atherosclerosis). Nicotine increases heart rate and blood pressure. The carbon monoxide in cigarette smoke replaces some of the oxygen in the blood, decreasing the amount of oxygen delivered to tissues, including the brain. Smoking also increases the risk of blood clots.(3,4)

  The risk associated with smoking is cut in half after one year without smoking, and it continues to decline until it's as low as a nonsmoker's risk.(35) According to AHA(8), the relative risk of stroke in heavy smokers (more than 40 cigarettes a day) is twice that of light smokers (less than 10 cigarettes per day). Stroke risk decreases significantly two years after cessation of cigarette smoking and is at the level of nonsmokers by five years.(58,(39,40), 79)

- **Physical Inactivity/Sedentary Lifestyle.** According to the American Heart Association, a person who is inactive is more likely to develop heart disease or have a stroke. Furthermore, regular, moderate to vigorous physical activity improves cardiovascular

fitness and helps reduce the risk of heart disease and stroke. Exercise can help control blood cholesterol, diabetes, and obesity. It can also help lower blood pressure.(7-9,11,12,35) Physical activity, whether it is sports, during leisure time or at work, and across whites, blacks, Hispanics, and males and females, has been related to reduced risk of ischemic stroke(41-45), reduced risk of hemorrhagic stroke(43,44), and reduced risk of stroke death.(41)

- **Obesity.** Too much body fat, especially if a lot of it is in the waist area, increases one's risk for health problems. These include high blood pressure, high blood cholesterol, high triglycerides, diabetes, heart disease, and stroke. Women with excess body fat are at higher risk of heart disease even if they don't have other risk factors.(7-9,11,12,35)
- **TIA or Previous Stroke.** If a person has already had a stroke or a transient ischemic attack, he or she has a 25 percent to 40 percent chance of having another stroke in the next 5 years. According to AHA(8), approximately 15 percent of all strokes are heralded by a TIA(8) People with TIAs have a short-term risk of stroke, hospitalization for cardiovascular events, and death. Of 1,707 TIA patients evaluated in the emergency department of a large healthcare plan(46), 180 patients, or 10 percent, developed stroke within 90 days. Ninety-one patients, or 5 percent, did so within 2 days. Predictors of stroke included: age >60 years; having diabetes mellitus; focal symptoms of weakness or speech impairment; and TIA lasting longer than 10 minutes.(46)
- **Myocardial Infarction and Other Heart Diseases.** People with coronary heart disease or heart failure have more than twice the stroke risk as people with hearts that work normally. Dilated cardiomyopathy (an enlarged heart), heart valve disease, and some types of congenital heart defects also increase the risk of developing blood clots in the heart that travel to the brain, which increases the risk of having a stroke.(35) According to AHA(8), the percentage of persons with a first MI who will have a stroke within five years is:
  - at ages 40 through 69, 4 percent of men and 6 percent of women.
  - at age 70 and older, 6 percent of men and 11 percent of women.
  - at ages 40 through 69, 3 percent of white men, 5 percent of white women, 8 percent of black men, and 9 percent of black women.
  - at age 70 and older, 6 percent of white men, 10 percent of white women, 7 percent of black men, and 17percent of black women.
- **Stress.** Too much stress over a long time, and unhealthy responses to it, may create health problems in some people. For example, people under stress may overeat, start smoking or smoke more than they otherwise would.(35)

- **Alcohol.** While moderate drinking, up to two drinks daily for men and one drink daily for women, is associated with a reduced risk of stroke, drinking more than this appears to increase stroke risk.(3,4) Drinking too much alcohol raises blood pressure, can cause heart failure, and can lead to stroke. It adds calories, contributes to obesity, and makes it harder to lose weight.(3,4,7-9,11,12,35)
- **Illegal Drugs.** Intravenous drug abuse carries a high risk of endocarditis (infection of the heart's lining or valves) and stroke. Cocaine use has been linked to heart attacks and strokes. Illegal drugs can be fatal even in first-time users.(3,4,35)
- **Migraine.** Some studies have found that people who have chronic headaches have an increased risk of stroke. However, since not all studies have found this association, additional research is needed to confirm this finding.(3,4)
- **Elevated homocysteine level.** Homocysteine, an amino acid and a building block of proteins, naturally occurs in the blood. Elevated levels of homocysteine can cause arteries to thicken and scar, making it more likely that cholesterol will clog arteries. B complex vitamins, B-6, B-12, and folic acid, have been shown to reduce blood levels of homocysteine. However, it isn't known whether taking supplements will reduce the likelihood of a TIA or stroke.(3,4)
- **Certain Blood Disorders.** Some blood disorders, such as sickle cell anemia, increase the risk of TIA or stroke because blood abnormalities can cause blood cells to be stickier and more likely to cling to artery walls, blocking them.(3,4) It's generally treated by removing blood cells or prescribing "blood thinners." Sickle cell anemia is a genetic disorder that mainly affects African Americans. Red blood cells are normally round, but in this disorder they become shaped like sickles. "Sickled" red blood cells are less able to carry oxygen to the body's tissues and organs. They also tend to get stuck or "clump" in small blood vessels. This can block arteries to the brain and cause a stroke.(35) Sickle cell disease is the leading cause of ischemic stroke among African American children.(40)
- **Carotid or Other Artery Disease.** The carotid arteries in the neck supply blood to the brain. A carotid artery narrowed by fatty deposits (plaque) from atherosclerosis may become blocked by a blood clot. In this case, the plaque in carotid arteries can build up and cause the carotid arteries to become very narrow. Blood clots in the carotid arteries can then collect and form clots. The clots can block the carotid artery where they are formed, as in thrombosis, or they can dislodge and get trapped in arteries closer to the brain, as in an embolism. Carotid endarterectomy may be performed to remove the plaque buildup. In addition, peripheral artery disease is the narrowing of blood vessels carrying blood to leg and arm muscles. People with this problem have a higher risk of carotid artery disease, which raises their risk of stroke.(35)

Another disorder in which the arteries that carry blood throughout the body do not develop as they should is Fibromuscular Dysplasia (FMD). In 75 percent of patients, FMD affects the arteries that supply blood to the kidneys. But it can also affect the carotid and other arteries, such as those to the arms and legs or to the abdomen.(35)

- **Peripheral artery disease.** In peripheral artery disease, fatty deposits build up on the artery walls in the legs and arms, narrowing the arteries. Anyone with peripheral artery disease has an increased risk of carotid artery disease, which increases stroke risk.(3,4)
- **Atrial Fibrillation (AF).** This heart rhythm disorder raises the risk for stroke. The heart's upper chambers quiver instead of beating effectively, which lets the blood pool and clot. If a clot breaks off and enters the bloodstream, it can lodge in an artery leading to the brain. The embolism originating from the heart can cause a stroke if it gets trapped in an artery close to or in the brain. Atrial fibrillation can be treated with drugs, such as aspirin or warfarin to keep clots from forming.(35) According to AHA(8), AF is an independent risk factor for stroke, increasing risk about five-fold.(47)
- **Sleep apnea.** People with this sleep disorder seem to have a higher risk of TIA or stroke, which may be because people with sleep apnea also seem to have an increased risk of high blood pressure, a known risk factor for stroke.(3,4)
- **Pregnancy.** According to the Baltimore–Washington Cooperative Young Stroke Study(48), the risk of ischemic stroke or intracerebral hemorrhage during pregnancy and the first six weeks postpartum is 2.4 times greater than for non-pregnant women of similar age and race. The risk of ischemic stroke during pregnancy is not increased during pregnancy per se, but increased 8.7-fold during the six weeks postpartum. Intracerebral hemorrhage showed a relative risk of 2.5 during pregnancy but increased dramatically to a relative risk of 28.3 in the six weeks postpartum. The excess risk of stroke (all types except subarachnoid hemorrhage) attributable to the combined pregnant/post-pregnant period was 8.1 per 100,000 pregnancies.(48) Swedish researchers found similar results, and noted that the three days surrounding delivery are the time of highest risk.(49) In the 2000–2001 U.S. Nationwide Inpatient Sample(38), the rate of stroke events per 100,000 pregnancies was 9.2 for ischemic stroke, 8.5 for intracerebral hemorrhage, 0.6 for cerebral venous thrombosis, and 15.9 for the ill-defined category of pregnancy-related cerebrovascular events, or a total rate of 34.2/100, 000, not including subarachnoid hemorrhage. The risk was greater for African Americans and among older women. Death occurred during hospitalization in 4.1 percent of women with strokes and in 22 percent of survivors after discharge to a facility other than home.(50)
- **Birth Control Pills.** Today's low-dose oral contraceptives carry a much lower risk of heart disease and stroke than the early pill did. However, women on the pill who smoke or have high blood pressure are at higher risk for cardiovascular disease. Taking oral contraceptives and smoking greatly increases the risk of heart attack. Women over age 35

who have not reached menopause and want to use birth control should talk with their healthcare provider about their personal and family medical history; risk factors for heart disease, stroke, and cancer; and the safety and effectiveness of the various birth control methods.(35)

- **Post-menopause.** Stroke is a major health issue for women, particularly for postmenopausal women, which raises the question of whether increased incidence is a result of aging or hormone status and whether hormone therapy affects risk. Furthermore, clinical trial data indicate that estrogen plus progestin, as well as estrogen alone, increase stroke risk in postmenopausal, generally healthy women, and provide no protection for women with established heart disease.(63,70)(51,52)
  http://circ.ahajournals.org/cgi/content/full/115/5/e69 - R45-179730#R45-179730

  http://circ.ahajournals.org/cgi/content/full/115/5/e69 - R41-179730#R41-179730Among postmenopausal women who are generally healthy, the Women's Health Initiative primary prevention clinical trial of 16,608 women (95 percent of whom had no pre-existing cardiovascular disease [CVD]) found that estrogen plus progestin increased ischemic stroke risk by 44 percent, with no effect on hemorrhagic stroke. The excess risk was apparent in all age groups, in all categories of baseline stroke risk, and in women with and without hypertension or prior history of CVD.(51) The trial also found that conjugate equine estrogen alone increased risk of ischemic stroke by 55 percent and had no significant effect on hemorrhagic stroke. The excess risk of total stroke conferred by estrogen alone was 12 additional strokes per 10,000 person-years.(51)

  In postmenopausal women with known chronic heart disease (CHD), the Heart and Estrogen/progestin Replacement Study (HERS), a secondary CHD prevention trial, found that a combination of estrogen plus progestin (conjugated equine estrogen [0.625 mg] and medroxyprogesterone acetate [2.5 mg]) hormone therapy did not reduce stroke risk.(53)

- **Geographical Risk Factors: The Stroke Belt.** According to CDC, "Reasons for a geographic variation in the prevalence of risk factors for stroke are complex and might be attributed to a combination of factors (e.g., cultural norms for diet and exercise, poverty and lack of economic opportunity, social isolation, and regional differences in access to healthcare and preventive services).(17,54) The geographic distribution of racial/ethnic groups alone does not account for the geographic variation in stroke mortality.(17,54) To further define and explain the underlying causes of these differences, additional studies are needed, including small-area analyses, in-depth interviews, more precise prevalence estimates by race/ethnicity, quality-of-care assessments, and recorded health outcomes. One such study under way is the Reasons for Geographic and Racial Differences in Stroke Study (REGARDS), a national population-based, longitudinal study designed to

determine the causes of excess mortality in the southeast United States and among blacks."(17,55)

Protective Factors for Stroke

There is evidence that a healthy lifestyle is a deterrent to stroke. Based on the results from the Women's health study of more than 37,000 women aged 45 or older, it seems that a healthy lifestyle, consisting of abstinence from smoking, low body-mass index (BMI), moderate alcohol consumption, regular exercise, and healthy diet were associated with a significantly reduced risk of total and ischemic stroke but not of hemorrhagic stroke.(56)

IV. Health Consequences of TIA and Stroke

A. General Overview of Health Consequences of TIA and Stroke

The National Institute on Aging of the National Institutes of Health (NIH)(57) summarizes the potential health consequences of having a stroke as follows:
"[Stroke damage] includes paralysis, problems with thinking, trouble speaking, and emotional problems. A common disability that results from stroke is complete paralysis on one side of the body, called hemiplegia. A related disability that is not as debilitating as paralysis is one-sided weakness, or hemiparesis. The paralysis or weakness may affect only the face, an arm, or a leg, or it may affect one entire side of the body and face. A stroke patient may have problems with the simplest of daily activities, such as walking, dressing, eating, and using the bathroom. Movement problems can result from damage to the part of the brain that controls balance and coordination. Some stroke patients also have trouble swallowing, called dysphagia. Stroke may cause problems with thinking, awareness, attention, learning, judgment, and memory. In some cases of stroke, the patient suffers a neglect syndrome. The neglect syndrome means that the stroke patient has no knowledge of one side of his or her body, or one side of the visual field, and is unaware of the problem. A stroke patient may be unaware of his or her surroundings, or may be unaware of the mental problems that resulted from the stroke. Stroke victims often have a problem forming or understanding speech. This problem is called aphasia. Aphasia usually occurs along with similar problems in reading and writing. In most people, language problems result from damage to the left hemisphere of the brain. Slurred speech due to weakness or incoordination of the muscles involved in speaking is called dysarthria, and is not a problem with language. Because it can result from any weakness or incoordination of the speech muscles, dysarthria can arise from damage to either side of the brain. A stroke can also lead to emotional problems. Stroke patients may have difficulty controlling their emotions or may express inappropriate emotions in certain situations. One common disability that occurs with many stroke patients is depression. Post-stroke depression may be more than a general sadness resulting from the stroke incident. It is a serious behavioral problem that can hamper recovery and rehabilitation and may even lead to suicide. Post-stroke depression is treated as any depression is treated, with antidepressant medications and therapy. Stroke patients may

experience pain, uncomfortable numbness, or strange sensations after a stroke. These sensations may be due to many factors, including damage to the sensory regions of the brain, stiff joints, or a disabled limb. An uncommon type of pain resulting from stroke is called central stroke pain or central pain syndrome or CPS. CPS results from damage to an area called the thalamus. The pain is a mixture of sensations, including heat and cold, burning, tingling, numbness, and sharp stabbing and underlying aching pain. The pain is often worse in the hands and feet and is made worse by movement and temperature changes, especially cold temperatures. Unfortunately, since most pain medications provide little relief from these sensations, very few treatments or therapies exist to combat CPS."(57)

The bottom line is that a stroke can affect a person emotionally, cognitively and physically. Health consequences may be mild or severe and brief or long lasting. The type of health consequence depends on the area of the brain affected by the stroke and the extent of the damage.

Some problems that happen after stroke are more common with stroke on one side of the brain than the other. In most people, the left side of the brain controls the ability to speak and understand language. The right side of the brain controls the ability to pay attention, recognize things people see, hear or touch, and to be aware of their own body. In some left-handed people, language is controlled by the right side of the brain and awareness by the left side of the brain.(58)

Having a stroke affects a person's ability to do everyday activities. Doing everyday activities may be difficult. These everyday activities may include:

- eating
- bathing
- getting dressed
- using the toilet
- doing housework
- using the telephone
- driving
- handling money
- writing
- speaking
- coordinating body movements

Functional Limitations

In 1999, more than 1.1 million American adults reported difficulty with such things as functional limitations and activities of daily living as a result of stroke.(59) The length of time to recover from a stroke depends on its severity. From 50 percent to 70 percent of stroke survivors regain functional independence, but 15 percent to 30 percent are permanently disabled, and 20 percent require institutional care at three months after onset.(60)

In the National Heart, Blood, and Ling Institute's (NHLBI) Framingham Heart Study (FHS), among ischemic stroke survivors who were at least 65 years of age, these disabilities were observed at six months after stroke(61):

- 50 percent had some hemiparesis.
- 30 percent were unable to walk without some assistance.
- 26 percent were dependent in activities of daily living.
- 19 percent had aphasia.
- 35 percent had depressive symptoms.
- 26 percent were institutionalized in a nursing home.

Recurrent Strokes

Of those who have a first stroke, the percentages with a recurrent stroke in five years are as follows(7):

- At 40 to 69 years of age: 13 percent of men and 22 percent of women.
- At ≥70 years of age: 23 percent of men and 28 percent of women.
- At 40 through 69 years of age: 15 percent of white men, 17 percent of white women, 10 percent of black men, and 27 percent of black women.
- At ≥70 years of age: 23 percent of white men, 27 percent of white women, 16 percent of black men, and 32 percent of black women.

Myocardial Infarction

Authors of the *Risk of Further Acute Vascular Events Following an Initial Myocardial Infarction or Stroke*, a Road Safety Research report for the Department of Transport of London, examined 260 English papers based on data beginning in 1995 to examine evidence on the occurrence of an MI) following a stroke. They indicated that there was too much variation in the studies to develop a reliable estimate of risk of myocardial infarction after a stroke. However, their findings are as follows(62):

- **“Occurrence of MI three months post stroke.** There were no EU studies but there were two studies carried out in the USA. The rate of MI in these studies was 1.5 percent (2/134) for stroke/TIA and 0.8 percent (11/1327) for TIA.
- **Occurrence of MI six months post stroke.** There were no studies giving time to MI six months after a stroke.
- **Occurrence of MI 12 months post stroke.** There were four studies conducted in the EU (after 1995) looking at risk of MI one year after a stroke (56, 70, 82, 83). Two of these studies looked at ischemic stroke and were combinable (Q ¼ 0.001 p ¼ 0.9) giving an odds of survival of 41.196 (16.9–100) or 98 percent (95 percent CI: 94–99 percent) or two people in 100 have an MI one year after an ischemic stroke. There was one study looking at stroke/TIA which found a rate of MI of 5.6 percent (4/71) and one study looking at a mixture of stroke types and the rate of MI was found to be 0.6 percent (1/157).
- **Occurrence of MI 24 months post stroke.** One study carried out in Germany looking at ischemic stroke. The risk of MI after two years was 1.2 percent (7/563) in this study. There was one study carried out in the Netherlands looking at stroke/TIA. The risk of MI was 4.3 percent (5/115).
- **Occurrence of MI at three years post stroke.** There was one study carried out in the Netherlands looking at stroke/TIA (after 1995), the rate was 1.5 percent (2/128).”(62)

Seizures

Cerebrovascular disease is a cause of epilepsy, especially in elderly people. Seizures complicate a clinical stroke and cause further impairment and despair for the patient. Seizures may also have implications for returning to work and driving.(63)

In 1997, Dr. Burn and other doctors from the Rehabilitation Research Unit, Southampton General Hospital, Southampton, England, wanted to describe the immediate and long-term risk of epileptic seizures after a first-ever stroke. They designed and conducted a cohort study to follow up stroke survivors for 2 to 6.5 years and to compare age-specific incidence rates of epileptic seizures of stroke survivors and in the general population. Data were gathered from a community-based stroke register. There were 675 patients with a first stroke who were followed for a minimum of two years. The main outcome variable was the occurrence of single and recurrent seizures.(63)

The frequencies associated with seizure onset and post-stroke seizures are indicated in Table 1. In summary, patients with a first-ever stroke had a 2 percent risk of having a seizure at stroke onset and an 11 percent risk of having a later seizure in the first five years of follow up. Patients with intracerebral and subarachnoid hemorrhage were at higher risk of seizures after stroke. Survivors who were independent at one month were at very low risk of future seizures.(63)

Table 10. Frequencies of Onset Seizures and Development of Post-stroke Seizures by Type of First Stroke(63)

Type of first stroke	No (%; 95% CI) of patients with onset seizures	Number (%) of patients with onset seizures who developed post stroke seizures
Cerebral infarction (n = 545)	10 (2; 0.9 to 3.4)	4 (40)
Primary intracerebral hemorrhage (n = 66)	2 (3; 0.4 to 10.5)	1 (50)
Subarachnoid hemorrhage (n = 33)	2 (6; 0.7 to 20.2)	0
Unknown (n = 31)	0 (0; 0 to 11.2)	0
Total (n = 675)	14 (2; 1.1 to 3.5)	5 (36)

In October 1998, Kathy Kaye and the University of Western Ontario Evidence Based Neurology Group wanted to answer the following questions: "What is the overall risk of developing a seizure after a stroke? Which stroke patients are at higher risk? What is their long-term prognosis? (e.g., seizure recurrence)?"(64)

To answer these questions, the authors used two existing studies as evidence: a) a cohort study following 675 post-stroke patients in the Oxfordshire community for a minimum of two years and a maximum of 6.5 years in which data were based on a community-based stroke register, and b) a prospective study of 1,195 consecutive patients admitted to a stroke service in Copenhagen where all patients stayed in the hospital until rehabilitation was no longer required. Data from Oxfordshire Community Stroke Project and Author Interpretation are presented in Table 3. The authors listed the following clinical bottom lines:

- 'The overall risk of developing a post-stroke seizure is 5.7 percent (3.5–7.9) at one year, and 11.5 percent (4.8–18.2) at five years.
- Most seizures (~85 percent) occur within 72 hours of a stroke. Patients with severe or hemorrhagic strokes are at higher risk.
- Single seizures occur in almost half (40 percent to 48 percent) of patients.
- The relative risk of seizure in stroke patients relative to the general population is 35.2 in the first year after a stroke.
- The risk of seizures at stroke onset is 2 percent (typically partial or secondarily generalized seizures). In these patients, the risk of subsequent seizures in 36 percent.
- Patients with intracerebral hemorrhages and subhemorrhages are at a higher risk of developing seizure, but this may be because of the initial stroke severity rather than stroke type.
- Post-stroke seizures are not related to mortality.
- Stroke survivors who function independently at one month are at very low risk of future seizures.'(64)

Table 11. Data from Oxfordshire Community Stroke Project and Interpretation(64)

Time after Sstroke	Risk of first seizure by type of stroke				Risk of recurrent seizure
	Cerebral infarction	1° Intracerebral haemorrhage	Subarachnoid haemorrhage	Total	
	545 patients	66 patients	33 patients	675 patients	675 patients
<24 hrs	2%(0.9-3.4)	3%(0.4-10.5)	6%(0.7-20.2)	2%(1.1-3.5)	36%
1 year	4.2%(2.2-6.2)	19.9%(1.5-38.3)	22%(2.6-41.8)	5.7% (3.5-7.9)	52-60%
2 years	6.7%(4.1-9.3)	19.9%(1.5-38.3)	27.8%(5.3-50.7)	8.2%(5.4-11)	
3 years	7.4%(4-10.8)	26.1%(2.2-50)	34.3%(8-62)	9.5%(5.8-13.2)	
4 years	8.6%(4.5-12.7)	26.1%(1.3-50.9)	34.3%(2-68.1)	10.5%(6-15)	
5 years	9.7%(3.7-15.7)	26.1%(0-54.8)	34.3%(0-100)	11.5%(4.8-18.2)	

V. Diagnosis and Screening for TIA and Stroke

Cerebrovascular events, such as TIAs and strokes, are medical emergencies. People experiencing a cerebrovascular event need to go to an emergency clinic or contact their doctor immediately so they can receive immediate and appropriate treatment. A prompt evaluation (within 60 minutes) is necessary to identify the cause of the episode and determine appropriate therapy.(5)

Although symptoms of a TIA generally resolve within one hour of onset and have no lasting adverse effects, it is still important that these patients seek medical treatment. Dr. Nina Solenski of American Family Physician states, “Transient ischemic attack is no longer considered a benign event but, rather, a critical harbinger of impending stroke. Failure to quickly recognize and evaluate this warning sign could mean missing an opportunity to prevent permanent disability or death. The 90-day risk of stroke after a transient ischemic attack has been estimated to be approximately 10 percent, with one half of strokes occurring within the first two days of the attack. The 90-day stroke risk is even higher when a transient ischemic attack results from internal carotid artery stenosis.”(6)

Cerebrovascular events are initially diagnosed through a careful history and physical examination. Because characteristics of TIAs include rapid onset, short duration, and the body’s return to its normal state, a doctor may diagnose a TIA based solely on the medical history of the event rather than on anything found during a general physical and neurological examination.

With regard to strokes, the most immediate goal is aggressive intervention to try to return blood flow back to the ischemic portions of the brain. This requires a quick determination of the cause of the stroke (ischemic vs. hemorrhagic), which is generally accomplished by computed tomography (CT) or magnetic resonance imaging (MRI). These tests are used to determine the size and location of the lesion, rule out bleeding, and identify the extent of the ischemic area of the brain. TIAs will not show lasting changes on CT or MRI scans whereas strokes will.(4) Although there are no laboratory tests that can confirm the presence of a TIA or stroke, routine blood work will be ordered to assess the patient’s baseline and provide information for subsequent treatment.

A variety of other tests may also be used to identify other problems that may have contributed to the cerebrovascular event. These include:

- *A full cardiac workup.*
- *Carotid doppler or ultrasonography*. A transducer sends high-frequency sound waves into the neck. After the sound waves pass through tissue and back, the doctor can analyze images on a screen to look for narrowing or clotting in the carotid arteries.
- *Computerized tomography angiography (CTA) scanning*. Scanning of the head may also be used to noninvasively evaluate the arteries in the neck and brain. CTA scanning uses X-rays, similar to a standard CT scan of the head, but may also involve injection of a contrast material into a blood vessel.
- *Magnetic resonance angiography (MRA).* This is a method of evaluating the arteries in the neck and brain. It uses a strong magnetic field, similar to MRI.
- *Transesophageal echocardiography (TEE).* During this procedure, a flexible probe with a transducer built into it is placed in the esophagus. Because the esophagus is directly behind the heart, very clear, detailed ultrasound images can be created, allowing a better view of some things, such as blood clots, that might not be seen clearly in a traditional echocardiography exam.
- *Arteriography*. This procedure gives a view of arteries in the brain not normally seen in X-ray imaging. A radiologist inserts a catheter through a small incision, usually in the groin. The catheter is manipulated through major arteries into the carotid or vertebral artery. Then, the radiologist injects a dye through the catheter to provide X-ray images of the arteries in the brain.

Additional tests and procedures may also be ordered to check for other risk factors, such as hypertension, heart disease, diabetes, high blood lipids, vasculitis, and peripheral vascular disease.

NIH Stroke Scale to Assess Neurological Deficit

NIH has developed a scale called *The National Institutes of Health Stroke Scale* (NIHSS) which can be used to provide a quantitative measure of stroke-related neurologic deficit. The NIHSS was created originally to measure baseline data on patients in acute stroke clinical trials. Now, the scale is frequently used as a clinical assessment tool to collect data for patient care, evaluate and document neurological status in acute stroke patients, evaluate acuity of stroke patients, measure stroke severity, predict lesion size, determine appropriate treatment, and predict short- and long-term patient outcome. It can provide a common language for information exchanges among healthcare providers.(65)

According to NIH, "the scale is designed to be a simple, valid, and reliable tool that can be administered at the bedside consistently by physicians, nurses, or therapists. The NIHSS is a 15-

item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extra-ocular movement, motor strength, ataxia, dysarthria, and sensory loss. A trained observer rates the patient's ability to answer questions and perform activities. Ratings for each item are scored with 3 to 5 grades with 0 as normal, and there is an allowance for un-testable items. The single-patient assessment requires less than 10 minutes to complete. The evaluation of stroke severity depends upon the ability of the observer to accurately and consistently assess the patient."(66)

A black-and-white paper-and-pencil version of the NIH Stroke Scale is presented in Appendix I. A page-by-page version of the NIH Stroke Scale is presented in Appendix II. Electronic versions of the NIH Stroke Scale Booklet may be viewed at:

- http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale_Booklet.pdf and
- http://www.nihstrokescale.org/docs/HospitalStrokeScales.pdf.

Other stroke scales and clinical assessment tools include: *Barthel Index, Canadian Neurological Scale (CNS), Cincinnati Stroke Scale Glasgow Outcome Scale (GOS), Hunt & Hess Scale, Los Angeles Pre-hospital Stroke Screen (LAPSS), Mini-Mental State Examination (MMSE), Modified Rankin Scale NIH Stroke Scale (NIHSS), Scandinavian Stroke Scale, and Stroke Specific Quality of Life Measure (SS-QOL).(67)*

VI. Treatment Options for TIA and Stroke and Potential Side Effects

A. Immediate Treatment

The main goal of treatment for an acute cerebrovascular episode is to correct the abnormality and improve the arterial blood supply to the brain. It is important that people with stroke symptoms, including TIAs, obtain treatment very quickly (within 3 to 24 hours) to prevent occurrence of more disabling outcomes. The longer the blood supply to the brain is cut off, the more severe the cerebral damage may be.(7)

The best outcomes might be obtained if treatment occurs within three hours. Unfortunately, the median time from stroke onset to arrival in an emergency room is three to six hours, according to a study of at least 48 unique reports of pre-hospital delay time for patients with stroke, TIA, or stroke-like symptoms. The study included data from 17 countries, including the United States. Improved clinical outcomes at three months were seen for patients with acute ischemic stroke when intravenous thrombolytic treatment was started within three hours of the onset of symptoms.(68) Despite this knowledge of improved outcomes with shorter time between onset of stroke symptoms and treatment, there is evidence that this time varies by demographic variables such as race and gender, with minorities experiencing a greater delay in treatment.(69,70)

Lack of knowledge / don't seek medical care. Based on the NSA telephone survey mentioned above, only 64 percent of those with TIA saw a physician within 24 hours of the event. An

additional 3.2 percent of participants recalled symptoms consistent with TIA but did not seek medical attention. Only 8.2 percent correctly related the definition of TIA and 8.6 percent could identify a typical symptom. Men, nonwhites, and those with lower income and fewer years of education were less likely to be knowledgeable about TIA.(13) About half of all patients who experience a TIA fail to report it to their healthcare provider.(9)

As previously indicated, TIA needs to be treated to decrease associated risks including averting a stroke. About 15 percent of strokes are preceded by a TIA; following a TIA, the 30-day risk of stroke is 3 to 17.3 percent, highest within the first 30 days; and within a year of TIA, up to a quarter of patients die.(9) Considering the importance of getting treatment quickly (optimally within three hours) to avoid worsening outcomes, including recurrent TIAs and full-blown strokes, these findings of lack of knowledge about TIA and lack of medical-care-seeking behavior for TIAs are worrisome.

B. Hospital Discharge and Ambulatory Care Visits

According to the American Heart Association Heart Disease and Statistics—2008 Update, from 1979 through 2005, the number of inpatient discharges from short-stay hospitals with stroke as the first listed diagnosis increased 20 percent, to 895,000.(7) The following "facts" have been taken from this report:

- "2005 data from the Hospital Discharge Survey of the National Center for Health Statistics (NCHS) showed the average length of stay for discharges with stroke as the first-listed diagnosis was 5.2 days.(71)
- From 1980 through 1999, National Hospital Discharge Survey (NHDS) and NCHS found that hospital discharge rates for stroke increased for blacks and whites; in-hospital mortality rates decreased for both black and white patients. Generally, the risk of stroke hospitalization was more than 70 percent greater for blacks than for whites. Both groups were similar in terms of in-hospital mortality rates.(72) Note: Estimates by race, especially time trends, are affected by the increasing underreporting of race in the National Hospital Discharge Survey (NHDS)/NCHS.(73)
- In 1999–2000, National Ambulatory Medical Care Survey (NAMCS), National Hospital Ambulatory Medical Care Survey (NHAMCS), and NCHS estimated the number of ambulatory care visits for stroke at 3.0 million.(74)
- In 2003, men and women accounted for roughly the same number of hospital stays for stroke in the 18 to 44 year old age group. After age 65 years, women were the majority. Among 65- to 84-year-olds, 54.5 percent of stroke patients were women, whereas in the oldest age group, women constituted 69.7 percent of all stroke patients."(75)

C. Outpatient Rehabilitation

Data from the BRFSS (CDC) 2005 survey on stroke survivors in 21 states and the District of Columbia found that 30.7 percent of stroke survivors received outpatient rehabilitation. The findings indicated that the prevalence of stroke survivors receiving outpatient stroke rehabilitation was lower than would be expected if clinical practice guideline recommendations for all stroke patients had been followed. Increasing the number of stroke survivors who receive needed outpatient rehabilitation might lead to better functional status and quality of life in this population.(76)

Dysgraphia treatment. A doctor or speech language therapist can recommend the correct diet for a person who is having difficulty swallowing and ways to help the person swallowing, such as correct body and head positions, correct food textures, correct food quantity, and correct feeding utensils and containers. If a person cannot eat by mouth, s/he will need to get nutrients via a tube. A nasogastric feeding tube is passed through the nose and esophagus to the stomach and is used for short-term tube feedings. A gastrostomy tube is put through the abdominal wall into the stomach for long-term feedings when recovery is slow. Tube feedings need to be closely watched for any problems or adjustments.(58)

D. Medications

The most commonly prescribed medicines for the treatment and prevention of cerebrovascular disease are listed in Table 12. In addition to the medications shown here, many stroke patients also receive medications to treat high blood pressure, diabetes, or high cholesterol. The choice of medication depends on the person's individual condition.

Table 12. Commonly Used Medications for Cerebrovascular Disease Treatment and Prevention(77-79)

Drug Name and Type	Other Names	Used For
Aspirin / Antiplatelet	acetylsalicylic acid, ASA	Stroke prevention
Clopidogrel / Antiplatelet	Plavix®	Stroke prevention
Dipyridamole / Antiplatelet	Aggrenox®, Persantine®, others	Stroke prevention
Heparin / Anticoagulant	Calciparine®, Liquaemin®	Stroke prevention. Heparin is fast acting and is used over the short term in the hospital. It is used for certain blood-clotting disorders, certain arterial abnormalities, an abnormal heart rhythm, such as atrial fibrillation, or other heart problems.
Ticlopidine / Antiplatelet	Ticlid®	Stroke prevention
Tissue Plasminogen Activator / Thrombolytic	tPA, Activase®	Acute stroke treatment. The U.S. Food and Drug Administration (FDA) has approved the clot-dissolving drug tissue plasminogen activator (tPA) to treat strokes caused by blood clots. tPA dissolves the clot and restores blood flow to the brain. tPA carries a risk of bleeding in the brain, but its benefits seem to outweigh the risks when an experienced doctor uses it properly. This drug can be given intravenously or by arterial catheter, but not by mouth.

Drug Name and Type	Other Names	Used For
Warfarin / Anticoagulant	Coumadin®, others	Stroke prevention. Slower acting than Heparin and used over longer term. It is used for certain blood-clotting disorders, certain arterial abnormalities, an abnormal heart rhythm, such as atrial fibrillation, or other heart problems.

Antiplatelet Drugs

Antiplatelet drugs are the most common form of drug therapy for cerebrovascular disease. They are used to prevent clotting by decreasing the functioning/activity of platelets. Aspirin is the most extensively used antiplatelet medication. . It has been shown to reduce platelet adhesiveness and prevent the progression of a stroke as well as the recurrence of a stroke.(80) Aspirin is also the least expensive treatment with the fewest potential side effects. The main side effect of aspirin is peptic ulcer disease, and some patients are unable to tolerate long-term aspirin use because of these gastric side effects. Alternatives to aspirin include clopidogrel, dipyridamole, and ticlopidine.

Anticoagulant Drugs

Anticoagulants reduce the risk of cerebrovascular episodes by reducing the ability of clotting system proteins to form clots in the blood. Intravenous anticoagulation may be used during the acute stage of an ischemic or embolic stroke in an attempt to increase blood flow to the brain. The patient is then switched to oral warfarin after about 3 to 5 days. Anticoagulant drugs should never be used for hemorrhagic strokes as it would increase bleeding in the brain. Despite widespread use of anticoagulants, their use is controversial.(81) NINDS has sponsored several clinical trials to test the efficacy of anticoagulants versus antiplatelet drugs. In the Stroke Prevention in Atrial Fibrillation (SPAF) trial, researchers found that, although aspirin is an effective therapy for the prevention of a second stroke in most patients with atrial fibrillation, some patients with additional risk factors do better on warfarin. In another study, the Trial of Org 10127 in Acute Stroke Treatment (TOAST), the effectiveness of low-molecular weight heparin (Org 10172) in stroke prevention was tested. Results indicated that heparin anticoagulants were not generally effective in preventing recurrent stroke or improving outcomes.(80) There are also questions about the appropriateness of this type of therapy, given the increased risk of bleeding that may follow ischemic damage to brain tissue.

Thrombolytic Drugs

Thrombolytic drugs are used during the acute stroke phase in an attempt to dissolve blood clots and reperfuse the ischemic brain tissue. One of the most widely used thrombolytic drugs is recombinant tissue plasminogen activator (tPA). The severity of ischemic stroke is reduced when the drug is given within three hours of stroke onset.(78,79) Quick treatment with thrombolytic drugs not only improves the chances of survival, but may also reduce the amount of disability resulting from the stroke.(78,79) Whether people can still gain some benefit from receiving

thrombolytic drugs beyond three hours is uncertain. After too much time has passed, the risks of bleeding or other complications from this type of therapy begin to outweigh the potential benefits.(79) Regardless, improved clinical outcomes at three months were seen for patients with acute ischemic stroke when intravenous thrombolytic treatment was started within three hours of the onset of symptoms.(68)

TPA-type therapy is not for hemorrhagic stroke. Unfortunately, tPA may dramatically worsen a hemorrhagic stroke. Also, not everyone who has had an ischemic stroke is an ideal candidate for thrombolytic therapy. The ability of tPA-type agents to dissolve blood clots carries with it a risk of brain hemorrhage and bleeding elsewhere. Researchers are experimenting with other methods of administering tPA, such as dripping tPA directly on the clot and beaming the clot with ultrasound waves.(79)

Herbal Stroke Treatment

Vinpocetine is a synthetic derivative of a compound found in the periwinkle plant. It is available as a prescription drug in Europe and Japan and is sold as a dietary supplement in the United States. Some preliminary research suggests that vinpocetine may reduce some of the long-term cognitive impairments after an acute ischemic stroke, supposedly by improving blood flow to the brain. However, there have been few clinical studies that have examined its use for stroke. More research is needed to determine what role, if any, vinpocetine may play in the prevention and treatment of stroke. Side effects of vinpocetine may include upset stomach, vertigo, anxiety, nausea, facial flushing, sleep problems, and headache.(82)

E. Treating Heart Disease

Sometimes treating a stroke means treating the heart, because various kinds of heart disease can contribute to stroke risk. For example, damaged heart valves may need to be surgically treated or treated with anti-clotting drugs to reduce the chance of clots forming around them. Blood clots can also form in hearts with atrial fibrillation and arrhythmia.(83)

F. Surgery and Procedures

Many people with cerebrovascular disease can manage their condition through medications, but for some people, medications aren't enough. When an artery becomes significantly blocked, usually 70 percent or more, surgery may be recommended. This section discusses the various surgical procedures used to treat ischemic strokes and hemorrhagic strokes.

Surgical Procedures for the Treatment of Ischemic Strokes

Carotid Endarterctomy. In 2005, an estimated 103,000 inpatient endarterectomy procedures were performed in the United States. Carotid endarterectomy is the most frequently performed surgical procedure to prevent stroke (NHDS, NCHS).(7) A carotid endarterectomy is a surgical procedure in which a doctor removes fatty deposits from one of the carotid arteries, two main arteries in the neck supplying blood to the brain. In addition to the usual risks associated with any surgery, a

carotid endarterectomy itself can trigger a stroke or heart attack by releasing a blood clot or fatty debris, although surgeons now place filters (distal protection devices) at strategic points in the bloodstream to "catch" any material that may break free during the procedure.(79)

Two clinical trials supported by the National Institute of Neurological Disorders and Stroke (NINDS)(84) have identified specific individuals for whom the surgery is highly beneficial when performed by surgeons and in institutions that can match the standards set in those studies. The surgery has been found highly beneficial for persons who have already had a stroke or experienced the warning signs of a stroke and have a severe stenosis of 70 percent to 99 percent. In this group, surgery reduces the estimated two-year risk of stroke by more than 80 percent, from greater than 1 in 4 to less than 1 in 10. Surgery reduces the five-year risk of stroke by 6.5 percent for patients with 50 to 69 percent stenosis, compared with an 80 percent risk reduction for patients with greater than 70 percent stenosis. Patients with 50 percent stenosis or lower do not show enough benefit from endartarectomy to outweigh the risks of the procedure. The point at which surgery begins to confer a significant benefit seems to be around the time that the artery is 50 percent blocked.(84)

In another trial, carotid endarterectomy was found to be highly beneficial for persons who are symptom-free but have a severe stenosis of 60 percent to 99 percent. In this group, the surgery reduces the estimated 5-year risk of stroke by more than one-half, from about 1 in 10 to less than 1 in 20.(84)

Carotid and Intracranial Angioplasty and Stents. For atherosclerosis blocking the carotid arteries, angioplasty and stenting may be appropriate. Angioplasty is a procedure to widen a blocked artery and stents are small wire mesh coils that prop open the artery once it is widened to improve blood flow.Angioplasty and stenting are commonly used to widen narrowed heart arteries for treatment of coronary artery disease. The long-term effectiveness of carotid angioplasty and stenting for stroke treatment has not yet been determined, primarily because it is a fairly new procedure.(85)

Angioplasty and stenting of carotid arteries may be an appropriate stroke treatment or stroke prevention option for some people who have had a stroke or TIA but can't undergo carotid endarterectomy surgery, such as those with severe heart or lung disease, those who have had radiation for neck tumors, or those who have already had a carotid endarterectomy and experience new narrowing after surgery. Sometimes, carotid angioplasty and stenting is used when the location of the narrowing (stenosis) is difficult to access with endarterectomy.(85)

Carotid angioplasty uses only local anesthetic and a small incision in the groin, so recovery is generally faster than with traditional surgery. One of the more serious complications that can occur after angioplasty and stenting is a stroke from a blockage in the brain's arteries caused by a blood clot or other debris. To prevent this from happening, patients are given blood thinners and monitored closely.(85)

In 1998, the American Heart Association indicated that "although carotid angioplasty and stenting are less invasive than surgery, the risks of diagnostic carotid angiography alone with its attendant catheter manipulation are not trivial. In some reports the risks approach those of carotid endarterectomy. Before carotid [angioplasty] and stenting can be considered for wide use, morbidity and mortality rates must be clearly and definitively elucidated, and training criteria must be established."(86) In 2007, the Mayo Clinic indicated that "Since the procedure is fairly new, doctors don't yet know how effective carotid angioplasty with stenting is as a stroke treatment or at preventing future strokes. However, it shows promise for people who need intervention but can't have a carotid endarterectomy."(85) In 2008, there still does not seem to be definitive effectiveness data on carotid angioplasty.

Intracranial Stenting. While carotid artery disease is buildup of plaques in the neck's arteries, intracranial atherosclerosis refers to buildup of plaques further in the brain arteries inside the skull. Because these arteries are smaller and inside the skull, they're more difficult to access — but a new procedure called intracranial stenting may be an effective stroke treatment or stroke prevention option for people with severe disease.(85)

Intracranial stenting is similar to stenting the carotid arteries. Using a small incision in the groin, doctors thread a catheter through the arteries and into the brain. Sometimes they use angioplasty to widen the affected area first; in other cases, angioplasty is not used before stent placement. Compared with the carotid arteries, the arteries inside the brain are very small and make a lot of twists and turns, so they're somewhat difficult to navigate with a catheter. Because of this, intracranial stenting requires expertise and specialized equipment.(85)

New stents have been used the last few years that are more flexible than those used in heart arteries. They're also self-expanding, so that instead of using a balloon to open the stent, the doctor can position and open the stent without a balloon. This means less equipment on the catheter tip, making it easier to navigate through the brain's small arteries.(85)

Researchers are still determining long-term results with intracranial stenting. In one recent study, intracranial stent placement without angioplasty reduced the risk of stroke for two years after placement, when compared with those who took only medications. Because of the small artery size, there are a variety of complications that can occur because of injury to the blood vessel from the catheter, including an artery puncture, damage to the lining of the vessel causing an artery dissection, bleeding into the brain, and stroke from artery blockage.(85)

Intracranial stenting is not suitable for everyone. Most people who have intracranial artery narrowing have good results with medications—such as aspirin and blood thinners—and lifestyle changes. This procedure is recommended only for those with symptomatic intracranial atherosclerosis that is severe—70 percent blockage or more—and hasn't been helped by medical treatment. People with diabetes or who have blockages in arteries that can't be accessed with a catheter are not good candidates for this procedure.(85)

Hyperbaric Oxygen. According to the American Heart Association/American Stroke Association 2007 "Guidelines on the Treatment of Acute Ischemic Stroke,"(83) hyperbaric oxygen might be useful to treat selected patients with ischemic neurological symptoms caused by air embolism or Caisson disease (decompression sickness). A review of published studies did not find evidence that hyperbaric oxygen improved outcomes after ischemic stroke or brain injury, however.

Penumbra. A new treatment for stroke victims promises to suction out clogged arteries in hopes of stopping injury to the brain before it does permanent harm. Penumbra is a device newly approved by the FDA and the latest in a series of inside-the-artery attempts to boost recovery from stroke. Penumbra can be tried with patients up to eight hours after a stroke or if tPA treatment fails. So far, this treatment has caused few serious side effects, and about 42 percent of successfully treated patients showed significant recovery a month later.(78)

New ways to remove clots. Doctors are also exploring new ways to remove clots. In a catheter embolectomy, a catheter is threaded into one of the arteries that lead to the brain and used to remove clots. Patients may also receive thrombolytic drugs directly into these arteries via a catheter.(79)

Surgical Procedures for the Treatment of Hemorrhagic Strokes

Aneurysm clipping. A tiny clamp is placed at the base of the aneurysm, isolating it from the circulation of the artery to which it's attached. This can keep the aneurysm from bursting, or it can prevent re-bleeding of an aneurysm that has recently hemorrhaged.(79)

Coiling (aneurysm embolization). In an embolization procedure, a catheter is maneuvered into the aneurysm. A tiny platinum coil is pushed through the catheter and positioned inside the aneurysm. The coil fills the aneurysm, causing clotting and sealing the aneurysm off from connecting arteries.(79)

Surgical AVM removal. It is not always possible to remove an AVM if it is too large or located deep within the brain. Surgical removal of a smaller AVM from a more accessible portion of the brain, though, can eliminate the risk of rupture, lowering the overall risk of hemorrhagic stroke.

Other ways to remove or reduce AVMs. Other treatment options for AVMs include focused radiation or embolization, in which the small arteries supplying the blood to the AVM are blocked, shrinking the AVM.(79)

G. What is in the future for stroke treatment?

"Currently, studies are being done on additional drugs that dissolve clots. These drugs are administered either in the veins (like tPA) or directly into the clogged artery. The goal of these studies is to determine which stroke patients might benefit from this new and aggressive form of treatment. New medications are also being tested that help slow the degeneration of the nerve cells that are deprived of oxygen during a stroke. These drugs are referred to as "neuroprotective" agents, an example of which is sipatrigine. Another example is

chlormethiazole, which works by modifying the expression of genes within the brain. (Genes produce proteins that determine an individual's makeup.) Finally, stem cells, which have the potential to develop into a variety of different organs, are being used to try to replace brain cells damaged by a previous stroke. In many academic medical centers, some of these experimental agents may be offered in the setting of a clinical trial. While new therapies for the treatment of patients after a stroke are on the horizon, they are not yet perfect and may not restore complete function to a stroke victim."(87)

V. What is the Impact of Cerebrovascular Disease on a Person's Driving Ability?

A. Transient Ischemic Attack (TIA)

In 70 percent of cases, the symptoms of a TIA will resolve in less than 10 minutes, and in 90 percent they will resolve in less than four hours. Although TIA is a quick and temporary condition, traffic accidents only take seconds to occur. During the short TIA, people have various symptoms, and are often incapacitated in various ways. People should avoid driving or doing any activity in which a sudden onset of TIA symptoms could put them or others in danger.(3,4)

The following factors may be taken into consideration during an assessment of a patient's fitness to drive(88):

- permanent damage to vision
- problems with memory, judgment, and concentration
- slow reactions in an emergency
- spasm in a paralysed limb that cannot be controlled
- seizures or convulsions.

TIA symptoms, their descriptions, and potential corresponding effects on driving ability are presented in Table 13. One health outcome of a TIA is not indicated in Table 13 below, but it should be noted—death. Within a year, up to 25 percent of people who have had a TIA die. This percentage seems to be higher among people 65 and older.(40)

Table 13. TIA Health Consequences and Potential Impacts on Driving(3,4,88)

Health Consequences (short term)	Description	Potential impact on driving (short term)
Numbness	Sensory loss; paresthesias; tingling and numbness; loss of sensation.	Cannot steer or apply brakes as usual. Slower reaction time.
Weakness	A reduction in the strength of one or more muscles.	Cannot steer or apply brakes as usual. Slower reaction time.
Speech impairment	Language impairment; speech impairment; inability to speak; aphasia, problem with expressing or understanding written or spoken language; dysarthria; slurred speech	Inability to tell someone, including the police, what the problem is. In the case of aphasia, person may not understand directions or traffic signs.

Health Consequences (short term)	Description	Potential impact on driving (short term)
Changes in vision	Loss of vision, decreased vision, double vision.	Inability to see what is going on and where self and other cars are while driving.
Vertigo, dizziness, or lack of balance	Sensation that the person or the room is moving	Inaccurate perception of where person or car is may result in accident.
Lack of coordination or loss of coordination	Lack of coordination and irregularity of voluntary movements; coordination impairment; ataxia; clumsiness	Person may apply brakes when not needed or steer in an unintended direction or not be able to respond in a timely or constructive way.
Confusion	Inability to think with usual speed or clarity. When confused, difficulty focusing attention; may feel disoriented. Confusion interferes with a person's ability to make decisions.	Inability to make constructive decisions when driving. Slow reaction time.
Apathy or inappropriate behavior	Person may not care about anything or may act in ways that are out of character for the person.	May produce erratic or illogical behavior that could interfere with driving and with making decisions related to driving.
Excessive somnolence or drowsiness	A state of near- sleep , a strong desire for sleep, or sleeping for unusually long periods	May not "see" situations requiring fast response. May not apply brakes or steer as quickly as needed. Slow response time.
Agitation or psychosis	Person may get very angry very quickly or misperceive situations or other people's intents. May not have good / accurate reality testing.	May interfere with accurate perception of other drivers' intents and reasonable response. Poor reaction time.
Neglect syndrome	Inattention to surrounding environment, particularly to one side; if severe, patient may deny deficit or even deny own body parts.	Lack of attention to driving. Poor reaction time.

B. Strokes

Driving is a complex skill and the ability to drive safely can be challenged by changes in physical, emotional, and mental conditions. A stroke may cause temporary or permanent changes in some or all of these areas. If a person has a stroke, s/he may:

- have trouble turning the steering wheel or applying the brake;
- become easily frustrated or confused while driving;
- drift across lane markings into other lanes;
- have difficulty thinking clearly about the traffic.(89)

Below, health consequences of strokes and their potential negative effects on driving are divided into three tables: health consequences related to a stroke on either side of the brain, health consequences related to a stroke on the left side of the brain, and health consequences related to a stroke on the right side of the brain (see Tables 14, 15, and 16 for more detail).

Table 14. Health Consequences After a Stroke on Either Side of the Brain and Their Potential Impact on Driving(57,58,88,90)

Health Consequences	Description	Potential Impact on Driving
Visual field loss	May ignore or not be able to see anything to the right. May only eat from the left side of plate or read from the left side of a page. Loss of vision, decreased vision, or double vision. Trouble with visual perception.	May not be able to see well enough to drive. May not be able to see where other cars and trucks are in relation to self.

Health Consequences	Description	Potential Impact on Driving
Vertigo, dizziness, or lack of balance	Sensation that the person or the room (or the car) is moving.	Inaccurate perception of where car or person is or is going may result in an accident.
Sexuality concerns	May be related to anxiety about how one looks and associated feelings of rejection.	May not effect driving.
Sensation changes	Numbness or loss of feeling in different parts of the body.	May not be able to steer or put on brakes as quickly or as effectively as needed. Slow response time.
Memory Problems	May have poor memory. This may lead to problems retaining, blending, and recalling information.	May not remember where one is going or how to get there. May not remember driving laws and procedures.
Poor judgment Poor problem solving	May not know own limits. May act without thinking about the consequences of actions. May misinterpret situation. May be unable to judge, problem-solve, organize and use 'abstract' reasoning skills. May be unable to think with usual clarity or speed.	May make "bad" decisions while driving that could lead to a crash or worse. When confused, may have difficulty focusing attention on driving. Confusion can interfere with person's ability to make effective decisions.
Impulsivity	May act without planning ahead.	May make "bad" decisions while driving that could lead to a crash or worse.
Hemiparesis or hemiplegia	May have weakness, partial or complete paralysis on one side of the body or one arm or one leg. If the stroke was on the left side of brain, the right side of body will be affected. If the stroke was on the right side of brain, the left side of body will be affected.	May be unable to steer, put on brakes, or perform other physical driving tasks in a timely or effective manner.
Fatigue Excessive somnolence or drowsiness	Fatigue is normal as the body learns or relearns how to work. A state of near sleep, a strong desire for sleep, or sleeping for unusually long periods.	May not be able to drive long distances. May not "see" situations requiring a quick response. May have a slower reaction time.
Weakness	A reduction in the strength of one or more muscles.	May not be able to steer or put on brakes as usual. Slower reaction time.
Lack of endurance	May be unable to do a task or activity for a long period of time. Should get better as person gets stronger.	May not be able to drive long distances.
Dysphagia	Swallowing problem caused by weakness or loss of feeling in the tongue, lips, palate or throat. May have problems moving food around in mouth, with food sticking in the throat, and coughing or choking on liquids or solids.	Not really a problem for driving unless it occurs while driving, which may cause person to be distracted from driving.
Dysarthria	A speech problem caused by damage to the motor center in the brain. May have problems saying the right words. Weakness or lack of coordination in the lips, tongue, and mouth muscles may affect: voice, word pronunciation, speech rate, rhythm and resonance, ability to chew, suck, swallow, and breathe.	Not necessarily a problem for driving unless person is stopped by the police and needs to talk. Inability to tell someone, including the police, what the problem is.
Coordination problems, ataxia, clumsiness	May have reduced hand–eye coordination. When reaching for an object, an arm may waver or a hand may overshoot the object. Lack of coordination and irregularity of voluntary movements.	May be unable to steer, put on brakes, or perform other physical driving tasks in a timely or effective manner. Person may apply brakes when not needed or steer in an unintended direction or be unable to respond in a timely or constructive way.
Abnormal muscle tone	A nerve problem that can make movements slow and jerky. There are stages of muscle tone recovery: A limb or joint may be limp and floppy. A limb or joint may move on its own when the muscle tone starts to return, and it doesn't always do what the brain tells it do to. A limb or joint begins to respond to the brain.	May be unable to steer, put on brakes, or perform other physical driving tasks in a timely or effective manner.
Bladder changes, urinary incontinence	May have problems urinating (retention) or controlling urine, caused by damage to the parts of the brain that control the bladder. May also have an infection. Usually can regain normal control with rehabilitation.	Not really a problem for driving unless it occurs while driving, which may distract the person from driving.
Bowel changes, constipation	Constipation is the most common problem after a stroke. May be caused by lack of liquids or limited physical activity. Usually can regain regular bowel pattern.	Not really a problem for driving

Health Consequences	Description	Potential Impact on Driving
Cognitive problems	May have problems with memory, thinking, attention, or learning. For example, may have trouble following directions, get confused easily, be unable to keep track of the time and date, have trouble making decisions, have short-term memory loss. Because of cognitive problems, the person may do things that are not safe.	May have an inability to make constructive decisions when driving. Slow reaction time.
Emotional lability Agitation or psychosis	Loss of emotional control and changes in mood. Limited control over feelings and reactions. Loss of inhibition.	May interfere with accurate perception of other drivers' intents and reasonable response. Poor reaction time.
Depression, apathy, or inappropriate behavior or post-stroke depression	Feeling helpless, hopeless, and having poor self-esteem, which can be caused by chemical imbalances in the brain.	May interfere with accurate perception of other drivers' intentions and reasonable response. May interfere with motivation to drive safely or react quickly.
Anxiety	Feeling uneasy or anxious for no reason.	May distract a person from driving.
Central stroke pain or central pain syndrome (CPS)	May feel hot, cold, numbness, sharp stabbing pain, or underlying aching pain.	Inattention to driving if pain is severe.
Neglect syndrome	Inattention to surrounding environment, particularly to one side; if severe, patient may deny deficit or even person's own body parts. May have no knowledge of one side of body or one side of visual field.	Lack of attention to driving. Inadequate visual perception or field of vision. Poor reaction time.
Seizure disorder Epilepsy	Lack of consciousness and uncontrolled physical movement.	Would cause a total lack of attention to driving and inability to drive. Must adhere to DMV regulations.

Table 15. Health Consequences of Left-Sided Strokes and the Potential Impacts on Driving(57,88,90,91)

Health Consequences	Description	Potential Impact on Driving
Aphasia - problems speaking and understanding language (About 20 percent of stroke survivors have a loss of speech and language.)	Depends on the type and severity of the brain injury. May have problems with speaking, listening, reading, writing, dealing with numbers, and understanding speech, thinking of words when talking or writing.	Person may not understand or be able to read directions or traffic signs. Does not necessarily have to be a problem for driving, unless person is stopped by the police and needs to talk or needs directions. Person has an inability to tell someone, including the police, what the problem is.
Language apraxia	May know the right words but have problems forming words or putting sounds together. In mild apraxia, may have clear speech with inconsistent sound substitutions. In severe apraxia, speech may sound like jargon or person may only be able to repeat a single syllable or phrase.	Person may not understand or be able to read directions or traffic signs. Does not necessarily have to be a problem for driving unless person is stopped by the police and needs to talk or needs directions. Person has an inability to tell someone, including the police, what the problem is.

Table 16. Health Consequences of Right-Sided Stroke and Potential Impacts on Driving(57,88,90,92)

Health Consequences	Description	Potential Impact on Driving
Anomia	Inability to recognize faces or pictures of familiar people or objects.	May not remember driving signs or signals or their meaning.
Attention span	Unable to focus attention on a conversation or tasks for long periods of time.	May not be as attentive to driving as need be for safe driving.
Denial	May deny having had a stroke. May deny that paralyzed arm or legs belong to them.	May deny that s/he cannot use that part of the body to drive with. May benefit from use of adaptive equipment.

Health Consequences	Description	Potential Impact on Driving
Neglect	Inattention to surrounding environment, particularly to one side; if severe, patient may deny deficit or even person's own body parts. May have no knowledge of one side of body or one side of visual field. May ignore left side of body or environment. May not turn to the left and may not look toward the left side. May not recognize things that are on the left.	Lack of attention to driving. Inadequate visual perception or field of vision. Poor reaction time.
Perseveration	May have difficulty following instructions or answering many questions asked one right after the other. May repeat answers or movement even though a new instruction was given or a new question asked.	May distract from timely response and attention to driving.
Visual-spatial problems	May have problems judging distance, size, position, and rate of movement, and how parts relate to the whole.	May misjudge distances, which could result in accidents.

The most important consideration for driving after a stroke must be whether the person is able to drive safely, without putting self or other road users and pedestrians at risk. A doctor will be able to give guidance as to whether a person will be allowed to drive, but if there is any doubt, the person should arrange to be assessed with a full evaluation. The evaluation results should indicate whether the person is able to drive and give advice on the changes that would need to be made to the person's vehicle.(93)

The following factors will be taken into consideration when a person's fitness to drive is assessed:

- permanent damage to vision
- problems with memory, judgment, and concentration
- slow reactions in an emergency
- spasm in a paralysed limb that cannot be controlled
- seizures or convulsions.(94)

A complete evaluation is needed to determine if a person can drive safely. An evaluation might have two parts. The first part might be an occupational therapy evaluation (to be completed by physician) and the second part might be a "behind-the-wheel evaluation."(95)

An Occupational Therapy Evaluation includes:

- visual screening
- physical skills
- attention and concentration skills
- reaction time
- recognition and understanding of road signs and traffic regulations(95)

Behind-the-Wheel Evaluations can be completed if the patient has a current driver's license or active permit. Otherwise, evaluation by the State (if appropriate, pending occupational therapy evaluation results and doctor's recommendations) is needed. Behind-the-Wheel evaluations address a person's ability to:

- operate vehicle controls
- act quickly and accurately behind the wheel
- obey traffic laws and regulations(95)

Behind-the-Wheel evaluations will help determine if a person is fit to drive and will also help determine the need for special equipment and follow up training sessions.(95)

VII. Can Side Effects of Treatment for Cerebrovascular Disease Have an Impact on Driving Ability?

Side effects of treatments for cerebrovascular disease and their potential effects on driving are summarized in Table 17.

Table 17. Side Effects of Cerebrovascular Treatments and Their Potential Impacts on Driving(96-98)

Possible Treatment	Possible Side Effects	Potential Impact on Driving
Aspirin	Poisoning from an overdose of aspirin. Increased risk of Reye syndrome in children and teens). Daily use of aspirin can contribute to macular degeneration, the leading cause of blindness in older Americans. Deteriorate the lining of the gastrointestinal tract. Stomach ulcers.	Severe gastrointestinal pain or blindness can obviously interfere with driving, but the condition will be evident in advance of driving and a person who cannot see or has severe abdominal pain should opt not to drive.
Clopidogrel (Plavix) Ticlopidine (Ticlid) Glycoprotein IIb/IIIa inhibitors (in combination with angioplasty with or without stenting)	Abdominal pain, back pain, bronchitis, bruising and bleeding under the skin, chest pain, coughing, depression, diarrhea, difficulty breathing, dizziness, fatigue, fluid retention and swelling, flu symptoms, headache, high blood pressure, high cholesterol, indigestion, inflammation of the nasal passages, itching, joint pain, nausea, pain, purple discoloration of skin, rash, upper respiratory tract infection, urinary tract infection.	Per PDR Health(96),, the side effects cannot be anticipated. So, the unanticipated emergence of any of the side effects could interfere with driving. The most obvious results are poor perception, poor attention to driving, and poor reaction time associated with dizziness and difficulty breathing.
Aggrenox, a combination of low-dose aspirin and the anti-platelet drug dipyridamole	Abdominal pain, back pain, bleeding, diarrhea, dizziness, fatigue, headache, indigestion, joint pain, nausea, pain, and vomiting.	Per PDR Health(96), the side effects cannot be anticipated. So the unanticipated emergence of any of the side effects could interfere with driving. The most obvious results are poor perception, poor attention to driving, and poor reaction time associated with dizziness, fatigue, and vomiting. Joint pain may make it more difficult to steer and perform fine motor tasks while driving.
Heparin (shorter term) Warfarin (Coumadin) (longer term)	Hemorrhage: Signs of severe bleeding resulting in the loss of large amounts of blood depend on the location and extent of bleeding. Symptoms include: chest, abdomen, joint, muscle, or other pain; difficulty breathing or swallowing; dizziness; headache; low blood pressure; numbness and tingling; paralysis; shortness of breath; unexplained shock; unexplained swelling; weakness.	Per PDR Health(96), the side effects cannot be anticipated. So the unanticipated emergence of any of the side effects could interfere with driving. The most obvious results are poor perception, poor attention to driving, and poor reaction time associated with pain, dizziness, numbness and tingling, paralysis, shortness of breath, weakness, and unexplained shock while driving. Joint pain, paralysis, numbness, and weakness may make it more difficult to steer and perform fine motor tasks while driving.

Possible Treatment	Possible Side Effects	Potential Impact on Driving
Tissue Plasminogen Activator / Thrombolytic (TPA)	Bleeding or oozing from cuts or around the area of injection; allergic reaction; fever; low blood pressure; signs of bleeding from other sites within the body, such as blood in the urine, black tarry stools, nose bleeds, bleeding from the gums; swelling; and hemorrhaging, including brain hemorrhage and bleeding elsewhere.	Bleeding and hemorrhaging can certainly distract someone from driving. If too much blood is lost, the person will become unconscious and be unable to drive at all.
Angioplasty with or without stenting	Discomfort in groin site seems to be the most common negative side effect. Please see side effects of platelet inhibitors above or any other medications if these are used in combination with angioplasty. Patient should check with doctor before driving.	Once healed, the person should physically be able to drive after a certain amount of time recommended by a doctor—usually at least five days. Side effects of any medication taken should be considered.
Carotid endarterectomy	Neurological complications can result. Hemorrhage of the wound bed and swelling of the neck can occur. Rarely, the hypoglossal nerve can be damaged and can result in twitching of the tongue and paralysis of the affected side of the tongue.	Once healed, the person should physically be able to drive after a certain amount of time, recommended by a doctor. People may drive a car when they can move their head as easily as they did before surgery and are free of pain. They should not drive after taking narcotic pain medicine or sleeping pills.
Anti-hypertensive medications	Different drugs have different side effects: Beta-blockers have a risk of provoking type 2 diabetes and may worsen asthma symptoms. Central alpha agonists may cause sedation, drying of the nasal mucosa, and rebound hypertension. Other benefits and adverse reactions to hypertension medications are reported in The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.(97)	Sleepiness may prevent people from driving long distances and slow response time. Asthma attacks will certainly distract from driving. Please refer to the background documents for heart disease and diabetes for more detailed information about side effects and their potential negative effect on driving.
Medications to lower cholesterol	Different drugs have different side effects: HMG-CoA reductase inhibitors (statins) like Lovastatin may cause certain side effects such as constipation. Uncommon side effects include muscle pain, lack of energy, fatigue, unusual bleeding or bruising, fever, yellowing of skin or eyes, loss of appetite. Pravastatin and sivastin may cause the same side effects including heartburn, headache, swelling, loss of appetite, muscle pain, muscle tenderness, muscle weakness, flu-like symptoms, and nausea.(98)	Lack of energy and fatigue may prevent a person from driving long distances and from responding quickly to avoid an accident. Sudden heartburn and headaches may distract a person from the task of driving. Muscle pain, weakness, and tenderness may interfere with a person's ability to steer or apply brakes quickly as needed. Flu-like symptoms and nausea will distract from the task of driving. Please refer to the background documents for heart disease and heart attacks for more detailed information about side effects and their potential negative effect on driving.

TIA, Stroke and Driving Regulations

Current U.S. Federal Regulatory and Medical Advisory Criteria for CMV Operators

The FMCSA Regulations, found in 49 Code of Federal Regulations (CFRs) 301 through 399, cover businesses that operate CMVs in interstate commerce. The FMCSA regulations that pertain to physical qualification standards are found in 49 CFR 391 Subpart E. Currently, there are no physical qualification standards that speak specifically to individuals who have experienced a TIA or stroke; however, a number of physical qualification standards are relevant to such individuals in as much as they speak to a number of the physical and mental manifestations of a TIA or stroke. These physical qualification standards are as follows:

- (b) A person is physically qualified to drive a commercial motor vehicle if that person —
  - (b)(7) Has no established medical history or clinical diagnosis of rheumatic, arthritic, orthopedic, muscular, neuromuscular, or vascular disease which interferes with his/her ability to control and operate a commercial motor vehicle safely;

- (b)(8) Has no established medical history or clinical diagnosis of epilepsy or any other condition which is likely to cause loss of consciousness or any loss of ability to control a commercial motor vehicle;
- (b)(9) Has no mental, nervous, organic, or functional disease or psychiatric disorder likely to interfere with his/her ability to drive a commercial motor vehicle safely;
- (b)(10) Has distant visual acuity of at least 20/40 (Snellen) in each eye without corrective lenses or visual acuity separately corrected to 20/40 (Snellen) or better with corrective lenses, distant binocular acuity of at least 20/40 (Snellen) in both eyes with or without corrective lenses, field of vision of at least 70° in the horizontal meridian in each eye, and the ability to recognize the colors of traffic signals and devices showing standard red, green, and amber.

Current FMCSA Guidance to Medical Examiners

In 1988, the FMCSA published the outcome of a conference to review the current medical standards covering neurological disorders (see: http://www.fmcsa.dot.gov/facts-research/research-technology/publications/medreports.htm), which suggests information for patients with neurological disorders. Unlike standards, which are regulations that a medical examiner must follow, these proposals are recommendations that the medical examiner is advised to follow. While not law, the correspondence is suggestive for medical examiners as a standard of practice. In this section of the evidence report we address only cerebrovascular disease.

Executive Summary – Static Neurological Conditions

Recommendations are made for cerebrovascular disease, head and spinal cord injury, and static neuromuscular disease and peripheral neuropathy. Below we report on the recommendations as they pertain to cerebrovascular disease.

Cerebrovascular Disease

TIAs are associated with a high rate of recurrence during the first year. Therefore, this automatically precludes commercial driving for one year. After one year, certification would depend on interval history, general health, neurological examination, and compliance with the treatment program.

Intracerebral and Subarachnoid Hemorrhage caused by operated aneurysm or arteriovenous malformation (AVM) requires the in-depth examination described for infarction. In addition, a patient with an aneurysm or AVM that has ruptured and has not been surgically repaired should not be permitted to drive commercial vehicles.

Cerebrovascular disease (and seizures): unprovoked seizures will occur in 16 percent of these individuals within the next five years. Individuals with fixed deficit or examination following an

occluded cerebrovascular event should not be considered qualified to obtain a license to operate a commercial vehicle for five years. There is no sound data on the risks following intracerebral or subarachnoid hemorrhage, but it must be assumed that risks will be similar, and similar recommendations would apply.

Task Force I Report: Static Neurological Conditions

Transient Ischemic Attack/Minor Stroke

Because the recurrence rate of ischemic neurological symptoms is highest during the first year after TIA or minor stroke, no commercial driver should be permitted to return to driving until he/she has had a careful evaluation of the event and a treatment plan has been outlined by a physician. The drivers should not return to commercial driving within one year of a stroke. A decision for clearance after one year will depend on the interval history, general health, neurological examination, and compliance with the treatment regimen. This clearance should be done by a neurologist. Any driver with a deficit that requires special evaluation and screening should be recertified annually. In the event that the driver is receiving drugs that have potentially high rates of complications, such as bleeding tendencies with oral anticoagulants, he/she should not return to driving. In the event the driver is taking medications that have a potentially depressing effect on the nervous system, he/she should not be qualified to drive.

Embolic or Thrombotic Cerebral Infarction

Drivers with a recent cerebral infarction warrant an evaluation to determine the source of the stroke and to establish the appropriate medical, surgical, and rehabilitation regimen. As in patients with a TIA or minor stroke, these persons are at increased risk of recurrent attacks. Restrictions on commercial driving should, at a minimum, be the same as those for patients with a TIA.

Patients with embolic or thrombotic cerebral infarction also will have residual intellectual or physical impairments severe enough to prevent a return to commercial driving. Fatigue, prolonged work, and stress may exaggerate the neurological residuals from a stroke. Most recovery from a stroke will occur within one year of the event. Commercial drivers who wish to return to full work status should undergo a careful neurological examination at one year after the stroke that includes assessment of their cognitive abilities, judgment, attention, concentration, vision, physical strength, agility, and reaction time. If the neurological residuals from the cerebral infarction are sufficiently severe to interfere with any of the above, then the driver should not be allowed to return to commercial driving. Any driver with a deficit that requires special evaluation and screening should be recertified annually.

A number of patients with an embolic or thrombotic cerebral infarction will have complicating seizures. The likelihood of seizure recurrence is associated with the location of the associated lesions. The risk is increased primarily in individuals with lesions associated with cortical or subcortical deficits.

Intracerebral or Subarachnoid Hemorrhage

Patients with subarachnoid or intracerebral hemorrhage can have serious residual neurological deficits in cognitive abilities, judgment, attention, or physical skills. They should all have a neurological examination including psychometric testing at one year after the cerebrovascular event before being cleared for commercial driving. In particular, patients with aneurysmal subarachnoid hemorrhage should be carefully assessed for subtle residual impairments in cognitive skills. The return to commercial driving status for a person with a recent intracranial hemorrhage should be based on the same criteria as outlined for patients with cerebral infarctions. Further, a small number of patients with intracranial or subarachnoid hemorrhage, similar to conditions of embolic or thrombotic cerebral infarction, will have complicating seizures. Because there is no sound data on risk of seizure following intracranial or subarachnoid hemorrhage, it must be assumed that risks will be similar to those following embolic or thrombotic cerebral infarction. Thus, recommendations similar to those for infarction patients with complicating seizures also apply to hemorrhage patients with complicating seizures.

Drivers with an aneurysm or an arteriovenous malformation that has ruptured and that has not been surgically treated should not be cleared for commercial driving. Drivers whose aneurysm or arteriovenous malformation has been surgically treated can return to driving after one year, as long as they have met all other standards set forth. Any driver with a deficit that requires special evaluation and screening should be recertified annually.

Task Force IV Report: Episodic Neurological Conditions

Cerebrovascular Disease

Individuals with strokes resulting in vascular lesions involving the cerebellum and brain stem are not at increased risk for seizures. Individuals with occlusive cerebral vascular disease with fixed deficits involving areas other than the cerebellum and brain stem should not be considered qualified to obtain a license to operate a commercial vehicle for a five-year period following the episode. Evaluation by an appropriate specialist to confirm the area of involvement may be required for waiver of this restriction. There is no sound data on risks of seizure following intracerebral or subarachnoid hemorrhage, but it must be assumed that risks will be similar, and thus similar recommendations would apply. Further studies are needed to clarify other groups at low risk. Limitations following cerebrovascular insult other than seizure also will affect licensure for commercial driving. Patients with embolic or thrombic cerebral infarction or subarachnoid or intracerebral hemorrhage will also have residual intellectual or physical impairments severe enough to prevent a return to commercial driving. Commercial drivers who wish to return to full work status should undergo a careful neurological examination at one year following the incident. This examination should include assessment of cognitive abilities, judgment, attention, concentration, vision, physical strength, agility and reaction time. If the neurological residuals are sufficiently severe to interfere with any of the above, then the individual should not be allowed to return to commercial driving.

Additional information on Neurological Disorders and Commercial Drivers supported at http://www.fmcsa.dot.gov/rulesregs/medreports.htm

Medical Fitness Standards and Guidelines for Individuals Performing Transportation Safety in the United States

Current medical fitness standards and guidelines for individuals performing transportation safety in the United States are summarized in Table 18. Included in the table are pertinent rules and guidance for pilots, railroad workers, and merchant mariners.

Table 18. Standards and Guidelines for Neurologic Disorders from U.S. Government Transportation Safety Agencies

Condition	FAA* (all classes of airmen)	Railroad†	Merchant Mariner‡
Neurologic	Electronic Code of Federal Regulations (e-CFR) **Title 14: Aeronautics and Space** **Part 67 – Medical Standards and Certification** **Subpart B – First Class Airman Medical Certificate** § 67.109 Neurologic. Neurologic standards for a first-class airman medical certificate are: (a) No established medical history or clinical diagnosis of any of the following: (1) Epilepsy; (2) A disturbance of consciousness without satisfactory medical explanation of the cause; or (3) A transient loss of control of nervous system function(s) without satisfactory medical explanation of the cause. (b) No other seizure disorder, disturbance of consciousness, or neurologic condition that the Federal Air Surgeon, based on the case history and appropriate, qualified medical judgment relating to the condition involved, finds— (1) Makes the person unable to safely perform the duties or exercise the privileges of the airman certificate applied for or held; or (2) May reasonably be expected, for the maximum duration of the airman medical certificate applied for or held, to make the person unable to perform those duties or exercise those privileges. **Guide for Aviation Medical Examiners** **Decision Considerations** **Aerospace Medical Dispositions** **Item 46. Neurologic** A history or the presence of any neurological condition or disease that potentially may incapacitate an individual should be regarded as initially disqualifying. Issuance of a medical certificate to an applicant in such cases should be denied or deferred, pending further evaluation. A convalescence period following illness or injury may be advisable to permit adequate stabilization of an individual's condition and to reduce the risk of an adverse event. Applications from individuals with potentially disqualifying conditions should be forwarded to the AMCD. Processing such applications can be expedited by including hospital records, consultation reports, and appropriate laboratory and imaging studies, if available. Symptoms or disturbances that are secondary to the underlying condition and that may be acutely incapacitating include pain, weakness, vertigo or in coordination, seizures or a disturbance of consciousness, visual disturbance, or mental confusion. Chronic	With few exceptions, most railroads have no specific medical standards	PHYSICAL EVALUATION GUIDELINES FOR MERCHANT MARINER'S DOCUMENTS AND LICENSES BACKGROUND. a. Various regulations in Title 46, Code of Federal Regulations (CFR), Parts 10, 12, and 13 require individuals to be physically qualified to hold certain merchant mariner's licenses and documents. With the exception of visual acuity and color vision, these regulatory requirements are not specified. The physician conducting the physical examination makes the initial determination whether or not the seaman is "fit for duty," that is, physically qualified to carry out his or her duties and responsibilities. However, there are medical conditions that cannot be routinely detected during a physical examination, unless the mariner discloses the symptoms or conditions, such as sleep disorders. It is recommended that medical personnel conducting physicals question mariners about these areas. b. Regulation I/9 of the International Convention on Standards of Training, Certification, and Watchkeeping for Seafarers (STCW) requires each party to establish standards of medical fitness for seafarers. The medical standards listed in this NVIC are also the United States' standards for meeting the STCW's regulation. c. Without specific guidelines for conducting the examination, or without a general familiarity with and appreciation for the rigors of employment in the maritime environment, most medical personnel are unable to fully evaluate the applicant's medical qualifications; therefore, this NVIC provides guidance to assist medical personnel in conducting these examinations. 4. DISCUSSION. For a vessel to be operated safely, it is essential that the crewmembers be physically fit and free of debilitating illness and injury. The seafaring life is arduous, often hazardous, and the availability of medical assistance or treatment is generally minimal. As the international trend toward smaller crews continues, the ability of each crewmember to perform his or her routine duties and respond to emergencies becomes even more critical. b. All mariners should be capable of living and working in cramped spaces, frequently in adverse weather causing violent motion of the vessel. Extended workdays are common. All mariners must be able to participate in emergency evolutions such as firefighting or launching lifeboats or liferafts. Members of the deck and engine department must be capable of physical labor, climbing, and

<table>
<tr><th>Condition</th><th>FAA* (all classes of airmen)</th><th>Railroad†</th><th>Merchant Mariner‡</th></tr>
<tr>
<td></td>
<td>conditions may be incompatible with safety in aircraft operation because of long-term unpredictability, severe neurologic deficit, or psychological impairment.
The following lists the most common conditions of aeromedical significance, and course of action that should be taken by the examiner as defined by the protocol and disposition in the table. Medical certificates must not be issued to an applicant with medical conditions that require deferral, or for any condition not listed that may result in sudden or subtle incapacitation without consulting the AMCD or the RFS Medical documentation must be submitted for any condition in order to support an issuance of an airman medical certificate.
• Cerebrovascular Disease (including the brain stem)
Demyelinating Disease
Extrapyramidal, Hereditary, and Degenerative Diseases of the Nervous System
Headaches
Hydrocephalus and Shunts
• Infections of the nervous system
• Neurologic Conditions
• Other conditions
Presence of any neurological condition or disease that potentially may incapacitate an individual
Aerospace Medical Dispositions
Item 46. Neurologic - Cerebrovascular Disease (including the brain stem) [15]
<table>
<tr><th>Disease/ Condition</th><th>Class</th><th>Evaluation Data</th><th>Disposition</th></tr>
<tr><td>Cerebral Thrombosis;

Intracerebral or Subarachnoid Hemorrhage;

Transient Ischemic Attack (TIA)</td><td>All</td><td>Submit all pertinent medical records, current neurologic report, to include CHD Protocol, brain MRI, Bilat carotid ultra sound, name and dosage of medication(s) and side effects</td><td>Requires FAA Decision</td></tr>
<tr><td>Intracranial Aneurysm or Arteriovenous Malformation</td><td>All</td><td>Submit all pertinent medical records, current neurologic report, name and dosage of</td><td>Requires FAA Decision</td></tr>
</table>
</td>
<td></td>
<td>handling moderate weights (30-60 pounds).
c. An applicant for an entry level rating i.e., ordinary seaman, wiper, or steward's department (food handler), does not require a physical examination, but he or she
should have the agility, strength, and flexibility to:
1. Climb steep or vertical ladders
2. Maintain balance on a moving deck
3. Pull heavy fire hoses up to 400 feet, and have the ability to lift fully charged fire hoses
4. Rapidly don an exposure suit
5. Step over door sills of 24 inches in height, and
6. Open or close watertight doors that may weigh up to 56 pounds
An applicant with physical limitations who may not be able to perform the above actions may be issued a Merchant Marine Document (MMD) with suitable limitations.
Regional Examination Centers (REC) processing an applicant who is restricted in his or her abilities shall contact the National Maritime Center (NMC-4C) for the appropriate endorsement.
d. Enclosure (1) contains standards to guide physicians, physician assistants, and licensed nurse practitioners, in examining merchant seamen. It will also assist Coast Guard licensing personnel in evaluating an applicant's eligibility based on the findings.
e. These guidelines are just that—guidelines. They are not intended to be absolute or all encompassing. Some individuals may have other medical conditions or physical limitations that would render them incompetent to perform their duties aboard a vessel. Others may be quite capable of working at sea without posing a risk to themselves, their ship, or shipmates even though one of the listed conditions exists. Any cause for rejection is disqualifying only while the condition persists or is likely to cause disqualifying complications. While each applicant must be evaluated for his/her physical competence individually, the conditions described in enclosure (1) are those that have been considered disqualifying by the medical and maritime communities. Waivers may be considered where extenuating circumstances are such to warrant special consideration and it can be demonstrated that the applicant can perform safely the duties of the license or merchant mariner document. Requests for waivers will be submitted to the National Maritime Center (NMC-4C) by the REC for review and a final determination.
5. ACTION.
a. The guidelines contained in this circular apply to all merchant</td>
</tr>
</table>

Condition	FAA* (all classes of airmen)				Railroad†	Merchant Mariner‡
			medication(s) and side effects			marine physical examinations and should be provided to medical personnel for use in conjunction with the physical examination form (CG-719K or equivalent). b. All RECs should use this circular as a guide when evaluating physical examination results submitted by mariners in accordance with Title 46, CFR, Parts 10, 12, and 13. 1. The physical standards in this enclosure apply to an applicant for an original license as a deck officer, engineer officer, or pilot. The same standards apply to the upgrade or renewal of these licenses unless specifically noted. 2. An applicant for either issuance of an original Merchant Mariner Document (MMD) or renewal of an MMD must also meet physical standards. With the exception of an MMD for the entry-level ratings, the standards are the same that apply to issuance of a license. These standards are summarized below: a. ORIGINAL MMD ENDORSED AS ORDINARY SEAMAN, WIPER, STEWARDS DEPARTMENT FOOD HANDLER No physical required; however, applicants should have the agility, strength, and flexibility to: 1. Climb steep or vertical ladders 2. Maintain balance on a moving deck 3. Pull heavy fire hoses up to 400 feet and have the ability to lift fully charged fire hoses 4. Rapidly don an exposure suit 5. Step over door sills of 24 inches in height 6. Open or close watertight doors that may weigh up to 56 pounds b. MMD ENDORSED AS ABLE SEAMAN Same physical requirements that apply to deck officer's licenses. c. RENEWAL OF MMD ENDORSED AS ABLE SEAMAN Same physical requirements for renewal of a deck officer's license. d. MMD ENDORSED AS QMED OR TANKERMAN Same requirements for original engineer's license. If the applicant has an unexpired engineer's license the physical exam may be waived. e. RENEWAL OF MMD ENDORSED AS QMED OR TANKERMAN Same physical requirements for renewal of an engineer's license. http://www.uscg.mil/hq/g-m/nvic/2_98/n2-98.pdf
	Intracranial Tumor[16]	All	Submit all pertinent medical records, current neurologic report, name and dosage of medication(s) and side effects	Requires FAA Decision		
	Pseudotumor Cerebri (benign intracranial hypertension)	All	Submit all pertinent medical records, current neurologic report, name and dosage of medication(s) and side effects	Requires FAA Decision		
	[15] Complete neurological evaluations supplemented with appropriate laboratory and imaging studies are required of applicants with the above conditions. Cerebral arteriography may be necessary for review in cases of subarachnoid hemorrhage. [16] A variety of intracranial tumors, both malignant and benign, are capable of causing incapacitation directly by neurologic deficit or indirectly through recurrent symptomatology. Potential neurologic deficits include weakness, loss of sensation, ataxia, visual deficit, or mental impairment. Recurrent symptomatology may interfere with flight performance through mechanisms such as seizure, headaches, vertigo, visual disturbances, or confusion. A history or diagnosis of an intracranial tumor necessitates a complete neurological evaluation with appropriate laboratory and imaging studies before a determination of eligibility for medical certification can be established. An applicant with a history of benign supratentorial tumors may be considered favorably for medical certification by the FAA and returned to flying status after a minimum satisfactory convalescence of 1 year. **Guide for Aviation Medical Examiners** **Application Process for Medical Certification** **Applicant History - Item 18. Medical History** **I. Neurological disorders; epilepsy, seizures, stroke, paralysis, etc.** The applicant should provide history and treatment, pertinent medical records, current status report and medication. The Examiner should obtain details about such a history and report the results. An established diagnosis of epilepsy, a transient loss of control of nervous system function(s), or a disturbance of consciousness is a basis for denial no matter how remote the history. Like all other conditions of aeromedical					

Condition	FAA* (all classes of airmen)	Railroad†	Merchant Mariner‡
	concern, the history surrounding the event is crucial. Certification is possible if a satisfactory explanation can be established. (See Item 46) **Examination Techniques** **Item 46. Neurologic** A neurologic evaluation should consist of a thorough review of the applicant's history prior to the neurological examination. The Examiner should specifically inquire concerning a history of weakness or paralysis, disturbance of sensation, loss of coordination, or loss of bowel or bladder control. Certain laboratory studies, such as scans and imaging procedures of the head or spine, electroencephalograms, or spinal paracentesis may suggest significant medical history. The Examiner should note conditions identified in Item 60 on the application with facts, such as dates, frequency, and severity of occurrence. A history of simple headaches without sequela is not disqualifying. Some require only temporary disqualification during periods when the headaches are likely to occur or require treatment. Other types of headaches may preclude certification by the Examiner and require special evaluation and consideration (e.g., migraine and cluster headaches). One or two episodes of dizziness or even fainting may not be disqualifying. For example, dizziness upon suddenly arising when ill is not a true dysfunction. Likewise, the orthostatic faint associated with moderate anemia is no threat to aviation safety as long as the individual is temporarily disqualified until the anemia is corrected. An unexplained disturbance of consciousness is disqualifying under the medical standards. Because a disturbance of consciousness may be expected to be totally incapacitating, individuals with such histories pose a high risk to safety and must be denied or deferred by the Examiner. If the cause of the disturbance is explained and a loss of consciousness is not likely to recur, then medical certification may be possible. The basic neurological examination consists of an examination of the 12 cranial nerves, motor strength, superficial reflexes, deep tendon reflexes, sensation, coordination, mental status, and includes the Babinski reflex and Romberg sign. The Examiner should be aware of any asymmetry in responses because this may be evidence of mild or early abnormalities. The Examiner should evaluate the visual field by direct confrontation or, preferably, by one of the perimetry procedures, especially if there is a suggestion of neurological deficiency. **Medical Certification Standards and Procedures Training (MCSPT) used as correspondence for AMEs and staff include:** **Item 18l: Neurological disorders; epilepsy, seizures, stroke, paralysis, etc.** Diagnosis of epilepsy or seizures is cause for disqualification no matter how remote the history. Applicants with a history of epilepsy MUST be medication and seizure free for 10 years before they can be considered for Special Issuance.		**Potentially disqualifying conditions** listed in the Physical Evaluation Guidelines for Merchant Mariner's Documents and Licenses including any disease or constitutional defect that would result in gradual deterioration of performance of duties, sudden incapacitation or otherwise compromise shipboard safety, including required response in an emergency situation. Neurologic guidelines and standards include the following: **NEUROLOGIC** • Any convulsive disorder resulting in an altered state of consciousness, regardless of control, by medication requires further evaluation. • Any condition that seriously limits balance or coordination (e.g. Parkinson's disease, chorea, Meniere's disease). o Chronic organic/traumatic brain syndrome o Neurosyphilis o Narcolepsy o Senility o Somnambulism

Condition	FAA* (all classes of airmen)	Railroad†	Merchant Mariner‡
	Neurological conditions that may incapacitate MUST be deferred. Other neurological conditions that may cause sudden incapacitation (other than seizure) are: 1. Multiple Sclerosis. 2. Myasthenia Gravis. 3. Muscular Dystrophy.. 4. Central nervous system tumors that affect neurologic functions. Generally Transient Ischemic Attacks (TIAs), strokes, Transient Global Amnesia, and Reversible Ischemic Neurological Defects require a two-year recovery period. Seizures (other than epilepsy) may require 2, 5, or 10-year recovery periods, seizure -free, off medication before an applicant can be considered for medical certification.		

* Source of information for FAA Regulations and Guidelines:
http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/special_iss/all_classes/glaucoma/
http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item52/amd/
http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item50/amd/

† Source of information for Federal Railroad Administration Guidelines:
http://www.fra.dot.gov/downloads/safety/hazmatch4.pdf

‡ Source of information for Merchant Mariner Guidelines:
http://www.uscg.mil/hq/g-m/nvic/2_98/n2-98.pdf

Regulatory Medical Fitness Standards in Various Countries

The effect of neurological disorders and impairments on CMV driving is widespread. Various countries globally have established regulatory medical fitness standards for the protection and safety of the public interest including licensed drivers. The medical standards of these countries are used to assess and determine the fitness of drivers operating CMVs. Likewise, neurological disorders are defined, and criteria for establishing these standards are constructed. Each country demonstrates its interpretation of neurological disorders through definition and by determining whom it affects. Regulatory standards and guidelines for neurological disorders and CMV driving in countries worldwide are presented in Table 19.

Table 19. Worldwide Guidelines for CMV Drivers with Neurological Disorders

Country	Reference	General
European Union	European Commission on Transport and Road Safety, Annex III to Directive 91/439/EEC; Council Directive 96/47/EC July 1996 amending Directive 91/439/EEC; IP/06/381 Member States Agree on the European Driving License 27 March 2006 ▪ Countries involved include: Austria*,Finland*, Sweden*, Belgium, Ireland, Denmark, Italy, Germany, Luxembourg, Greece, The Netherlands, Spain, Portugal, France, and The United Kingdom (29 July 1991) ▪ Member states had to apply directive 91/439/EEC by 1 July 1996. ▪ European member states have to stay within a Council directive: they can be more restrictive, but not more liberal. *added in Council Directive 96/47/EC July 1996	Driving licenses shall not be issued to, or renewed for, applicants or drivers suffering from a serious neurological disease, unless the application is supported by authorized medical opinion. Neurological disturbances associated with diseases or surgical intervention affecting the central or peripheral nervous system, which lead to sensory or motor deficiencies and affect balance and coordination, must accordingly be taken into account in relation to their functional effects and the risks of progression. In such cases, the issue or renewal of the license may be subject to periodic assessment in the event of risk of deterioration. Driving licenses shall not be issued or renewed for applicants or drivers suffering or liable to suffer from epileptic seizures or other sudden disturbances of the state of consciousness. Driving licenses shall be issued only to those applicants who have passed a test of skills and behaviour and a theoretical test and who meet medical standards, in accordance with the provisions of Annexes II and III
Canada	Determining Medical Fitness to Operate Motor Vehicles. CMA (Canadian Medical Association) Driver's Guide 7th edition. (2006)	Individuals who hav e experienced a stroke should not drive for at least 1 month. o Driving may resume if: o The physician notes no clinically significant motor, cognitive, perceptual, or vision deficits o Neurologic assessment discloses no obvious risk of sudden recurrence o Any underlying cause has been addressed with appropriate treatment, and o A post-stroke seizure has not occurred in the interim.
Australia	Assessing Fitness to Drive (For Commercial and Private Vehicle Drivers) Medical Standards for Licensing and Clinical Management Guidelines. Austroads and NTC (National Transport Commission) Australia (2006) Medical Standards for Licensing	The criteria for an *unconditional license* are NOT met: o if the person has had a stroke A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of an appropriate specialist, and the nature of the driving task, and subject to periodic review: o if the stroke was caused by a condition that has now been satisfactorily treated. A satisfactory recovery from the stroke, including perceptual deficits, must also be demonstrated. Transient Ischemic Attacks The criteria for an unconditional license are NOT met: o if the person has had two or more TIAs. A conditional license may be granted by the Driver Licensing Authority, taking into account the opinion of an appropriate specialist, and the

Country	Reference	General
		nature of the driving task, and subject to periodic review: o if the etiology of the attacks has been identified, the underlying cause removed, and the person has had a 6-month period free of attacks.
United Kingdom	At a Glance Guide to the current Medical Standards of Fitness to Drive (for Medical Practitioners) Issued by Drivers Medical Group. DVLA, Swansea (February 2007)	Cerebrovascular Disease: including stroke due to occlusive vascular disease, spontaneous intracerebral haemorrhage, TIA and amaurosis fugax. Group 2 Entitlement: Refusal/revocation for at least 12 months following a stroke or TIA. Can be considered for licensing after this period if there is a full and complete recovery and no other significant risk factors. Licensing will also be subject to satisfactory medical reports including exercise ECG testing.
New Zealand	Medical Aspects of Fitness to Drive: A Guide for Medical Practitioners. Land Transport Safety Authority. (May 2002)	**Transient ischaemic attacks (TIA):** should not drive for at least six months for a single TIA. Individuals who have multiple TIAs should not drive. However, the Director may consider granting a license where sound reasons exist. When driving should cease: Driving should cease for at least six months following a single attack subject to the cause being identified and satisfactorily treated, and a specialist medical assessment being carried out. Individuals who have multiple TIAs that impair consciousness or awareness, cause vertigo, or cause visual disturbances, should not drive. Licenses will generally not be issued to applicants with a history of TIAs. When driving may resume or may occur: The Director of Land Transport, or the Director's delegate, may consider applications from individuals who have had multiple TIAs after 12 months form the last attack if an appropriate specialist supports such an application. If a license is granted, conditions may be imposed that require the individual to be subject to regular medical assessment.
Sweden	Swedish National Road Administration Statute Book Effective 1/1/99	o A serious cognitive disturbance (including stroke) constitutes grounds for denial of possession. Disturbances in attention, judgment and memory, in visuospatial and psychomotor functions shall be taken into special consideration when making a medical assessment. The presence of emotional lability and increased fatiguability shall also be taken into consideration. o Due consideration shall be given to the additional risks and dangers to traffic safety involved in such possession. Reappraisal o Should occur at intervals considered suitable in each individual case.

Methods

The *Methods* section gives a synopsis of how we identified and analyzed information for this report. The section briefly covers the key questions addressed, literature searches performed, the criteria used including studies, evaluation of study quality, assessment of the strength of the evidence base for each key question, and methods used for abstracting and analyzing available data. Specific details of literature searches, study quality assessment, and statistical approaches used are documented in appendices.

Key Questions

This evidence report addresses three key questions. Each of these key questions was developed by the FMCSA so that the answers would provide information useful in updating its current medical examination guidelines. The three key questions addressed in this evidence report are:

Key Question 1: Are individuals who have experienced a stroke at an increased risk for a motor vehicle crash (crash risk or driving performance)?

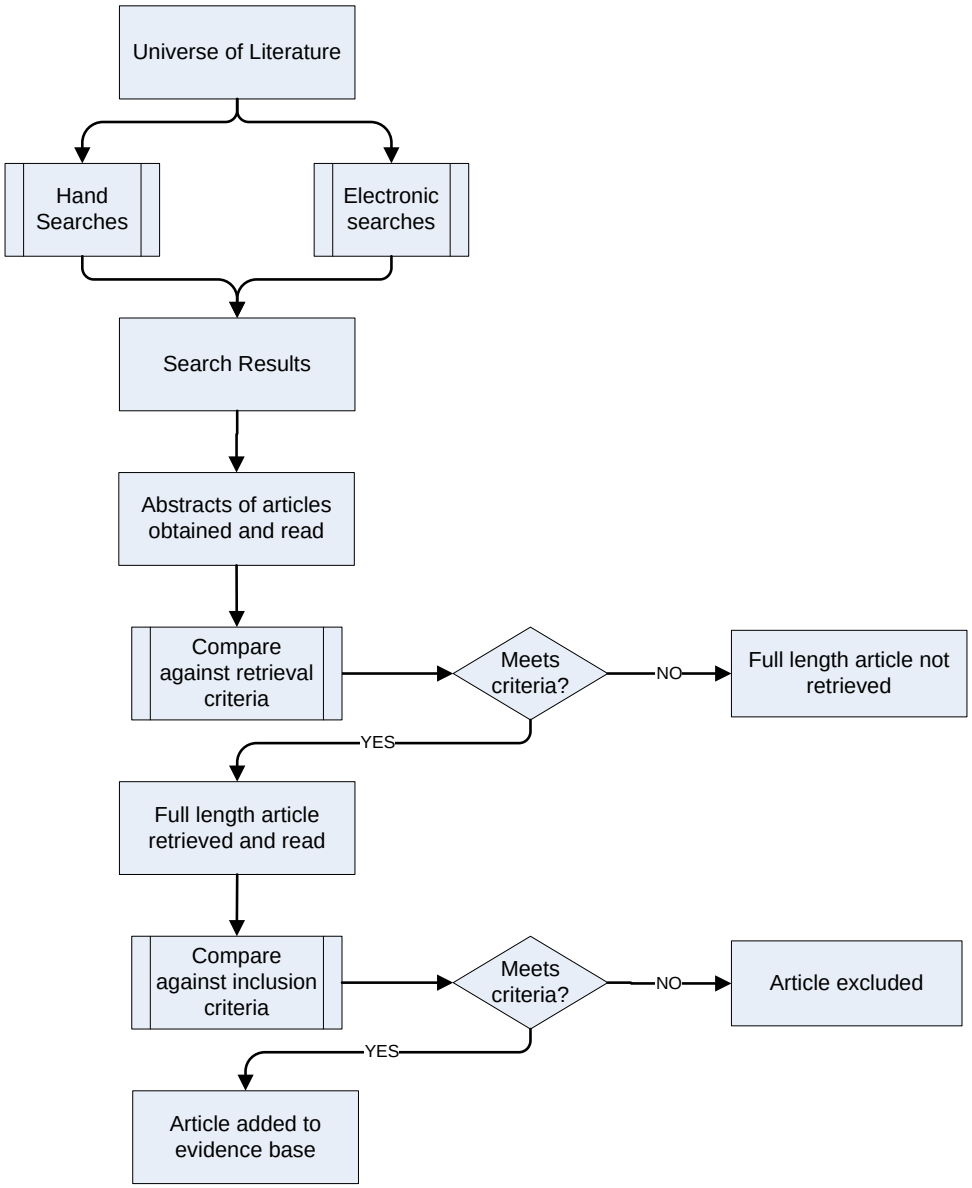
Key Question 2: If so, can neuropsychological testing of individuals who have experienced a stroke predict crash risk?

Key Question 3: Among individuals who have experienced a TIA, what is the risk of experiencing a future stroke?

Identification of Evidence Bases

The individual evidence bases for each of the three key questions addressed in this evidence report were identified using the multistage process captured by the algorithm presented in Figure 8. The first stage of this process consists of a comprehensive search of the literature. The second stage consists of the examination of abstracts of identified studies to determine which articles will be retrieved. The final stage of the process consists of the selection of the actual articles that will be included in the evidence base.

Figure 8. Evidence Base Identification Algorithm



Searches

One characteristic of a good evidence report is a systematic and comprehensive search for information. Such searches distinguish systematic reviews from traditional literature reviews, which use a less rigorous approach to identifying and obtaining literature, thereby allowing a reviewer to include only articles that agree with a particular perspective and to ignore articles that do not. Our approach precludes this potential reviewer bias because we obtain and include articles according to explicitly determined *a priori* criteria. Full details of the search strategies used in this report are presented in Appendix A.

Electronic Searches

We performed comprehensive searches of the electronic databases listed in Table 20.

Table 20. Electronic Databases Searched

Name	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 through January 10, 2008	OVID
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2007 Issue 4	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2007 Issue 4	www.thecochranelibrary.com
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2007 Issue 4	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2007 Issue 4	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through January 10, 2008	OVID
Health Technology Assessment Database (HTA)	Through 2007 Issue 4	www.thecochranelibrary.com
MEDLINE	1950 through September 12, 2007	OVID
National Guideline Clearinghouse	Searched December 13, 2007	www.ngc.gov
NHS Economic Evaluation Database (NHS EED)	Through 2007 Issue 4	www.thecochranelibrary.com
PsycINFO	Through January 10, 2008	OVID
PreMEDLINE	Searched January 10, 2008	OVID
TRIS	Searched December 18, 2007	

Manual Searches

We reviewed journals and supplements maintained in ECRI's collections of more than 1,000 periodicals. Non-journal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant reports not identified by our electronic searches. To retrieve additional relevant information, we also performed hand searches of the "gray literature." Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. The latter documents do not appear in the peer-reviewed journal literature.

Retrieval Criteria

Retrieval criteria were used to determine whether a full-length version of an article identified by our searches should be ordered. Decisions pertaining to whether a full-length article should be

retrieved are usually based on a review of available abstracts. For this project, retrieval criteria were determined *a priori* in conjunction with the FMCSA. The retrieval criteria are presented in Appendix B.

If an article did not meet the retrieval criteria for this evidence report, the full-length version of the article was not obtained. If it was unclear whether a potentially relevant article met our retrieval criteria (e.g., no abstract was available for evaluation), the full-length version of that article was be obtained.

Inclusion and Exclusion Criteria

Each retrieved article was read in full by an ECRI analyst who determined whether that article met a set of predetermined, question specific, inclusion criteria. As was the case for the retrieval criteria, the inclusion criteria for this evidence report were determined *a priori* in conjunction with the FMCSA. These inclusion and exclusion criteria are presented in Appendix C.

If on reading an article it was found not to meet the question specific inclusion criteria listed in Appendix C, the article was excluded from the analysis. Each excluded article, along with the reason(s) for its exclusion, are presented in Appendix D.

Evaluation of Quality and Strength of Evidence

Rather than focus on the quality of the individual studies that comprise an evidence base, our approach to assessing the quality of evidence focused on the overall *body* of the available evidence that was used to draw an evidence-based conclusion.(100) Using this approach, which is described briefly in Appendix E, we took into account not only the quality of the individual studies that comprise the evidence base for each key question, we will also consider the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Our approach to assessing the strength of the body of evidence makes a clear distinction between a qualitative conclusion (e.g., “Individuals with stroke are at increased risk for a motor vehicle crash”) and a quantitative conclusion (e.g., “When compared to individuals who did not have a prior TIA, the risk ratio for a stroke among individuals with a prior TIA is 12.02; 95 percent CI 5.66 to 25.53”). As shown in Table 21, we assigned a separate strength of evidence rating to each of type of conclusion. Evidence underpinning a qualitative conclusion was rated according to its strength, and evidence underpinning quantitative conclusions was rated according to the stability of the effect size estimate that was calculated.

Table 21. Strength of Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Minimally acceptable	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI recommends frequent monitoring of the relevant literature.
Insufficient	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI recommends frequent monitoring of the relevant literature.
Quantitative Conclusion (Stability of Effect Size Estimate)	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI recommends frequent monitoring of the relevant literature.

The definitions presented in the table above are intuitive. Qualitative conclusions that are supported by strong evidence are less likely to be overturned by the publication of new data than conclusions supported by weak evidence. Likewise, quantitative effect size estimates deemed to be stable are more unlikely to change significantly with the publication of new data than are unstable effect size estimates.

Statistical Methods

The set of analytic techniques used in this report was extensive. In summary, random- effects meta-analyses were used to pool data from different studies.(101-110) Important differences in the findings of different studies (heterogeneity) were identified using the Q-statistic and I^2.(106,111-116) Whenever appropriate, heterogeneity was explored using meta-regression techniques.(117-119) Sensitivity analyses, aimed at testing the robustness of our findings, were performed using cumulative random-effects meta-analyses.(120-126) All meta-analyses in this Evidence Report were performed using Comprehensive Meta-Analysis software.(127-129)

We calculated several different estimates of effect. The choice of effect size estimate depended on the purpose of the studies we assessed, their design, and whether reported outcome data were continuous or dichotomous. Between-group differences in outcome measured using continuous data were analyzed in their original metric (if all included studies reported on the same outcome using the same metric) or the data were standardized into a common metric known as the standardized mean difference (SMD). Dichotomous data were analyzed using the rate ratio (RR) or the odds ratio (OR). Time-to-event data were analyzed using the hazard ratio (HR). The formulae for these effect sizes and their variance are presented in Table 22. If means and

standard deviations were not available for continuous data, every effort was made to determine an estimate of treatment effect from reported statistics (e.g., t-values, f-values) or from p-values using methods described in detail elsewhere.(130)

Table 22. Effect Size Estimates Used in Evidence Report and their Variance

Effect size	Formula (Effect size)	Formula (Variance)
WMD	$\mu_{TG}-\mu_{CG}$	$\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2+(n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)\left(\frac{1}{n_{TG}}+\frac{1}{n_{cg}}\right)$
SMD	$\frac{\mu_{TG}-\mu_{CG}}{\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2+(n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)}$	$\frac{n_{TG}+n_{CG}}{n_{TG}n_{CG}}+\frac{SMD^2}{2(n_{TG}+n_{CG})}$
Where: μ_{TG} = mean (treatment group); μ_{CG} = mean (control group); S_{TG} = standard deviation (treatment group); S_{CG} = standard deviation (control group); n_{TG} = enrollees (treatment group); n_{CG} = enrollees (control group)		
Event Rate	$a/a+b$	$\ln\left[\frac{1}{a}+\frac{1}{a+b}\right]$
Where: a = number of individuals in cohort experiencing an event; b = number of individuals in cohort who did not experience an event		
RR (incidence)	$\left(\frac{a_{msd}}{pt_{msd}}\right)\Big/\left(\frac{b_{control}}{pt_{control}}\right)$	$\ln\left[\frac{1}{a_{msd}}+\frac{1}{b_{control}}\right]$
Where: a = number of individuals with disorder / who crashed; pt_{msd} = rate denominator (disorder grp); b = number of individuals without disorder / who crashed; $pt_{control}$ = rate denominator (control grp)		
OR	$\left(\frac{a}{b}\right)\Big/\left(\frac{c}{d}\right)=\left(\frac{ad}{bc}\right)$	$\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}$
RR	$\left(\frac{a}{a+c}\right)\Big/\left(\frac{b}{b+d}\right)$	$\frac{1}{a}+\frac{1}{a+c}+\frac{1}{b}+\frac{1}{b+d}$
Where: a = number of individuals with disorder who crashed; b = number of individuals without disorder who crashed; c = number of individuals with disorder who did not crash; d = number of individuals without disorder who did not crash.		
HR	$\frac{O_{pi}/E_{pi}}{O_{ci}/E_{ci}}$	$\exp\left(\ln\left[\frac{1}{E_{pi}}+\frac{1}{E_{ci}}\right]\right)$
Where O_{pi} = observed number of events in treatment group; O_{ci} = observed number of events in control group; E_{pi} = log rank expected number of events in treatment group; E_{ci} = log rank expected number of events in control group		

HR = hazard ratio; RR = rate ratio; OR = Odds Ratio; RR = rate ratio; SMD = standardized mean difference; WMD = weighted mean difference

Evidence Synthesis

Key Question 1: Are individuals who have had a stroke at an increased risk for a motor vehicle crash?

Introduction

Stroke, or cerebrovascular accident, is a sudden neurological deficiency resulting from cerebral infarction or hemorrhage. Stroke can cause outcomes ranging from long-term incapacitation to sudden death. In the United States, an estimated 400,000 people have first-time strokes annually.(131) Approximately 25% to 33% of strokes occur in people under the age of 65 years.(131,132) Men are more commonly affected than women. Additional risk factors include hypertension, smoking, heart disease, diabetes, and high cholesterol.(131) These risk factors are relatively common among CMV drivers(133), which may place CMV drivers at a greater risk of stroke than the general population. The results of two studies conducted in Denmark found that professional drivers were indeed at an increased risk of stroke.(134,135)

Stroke and its co-morbidities, complications, and treatments have the potential to increase the risk of motor vehicle crash. Psychomotor and neurocognitive deficits resulting from stroke affect most survivors(132) and could impair the safe operation of a motor vehicle. Individuals who have had a stroke may also be at greater risk for a subsequent stroke, which could result in sudden incapacitation (although the risk of sudden incapacitation due to stroke is thought to be rare(132)) or further disability. For these reasons, a history of stroke may be of concern when considering safe motor vehicle operation.

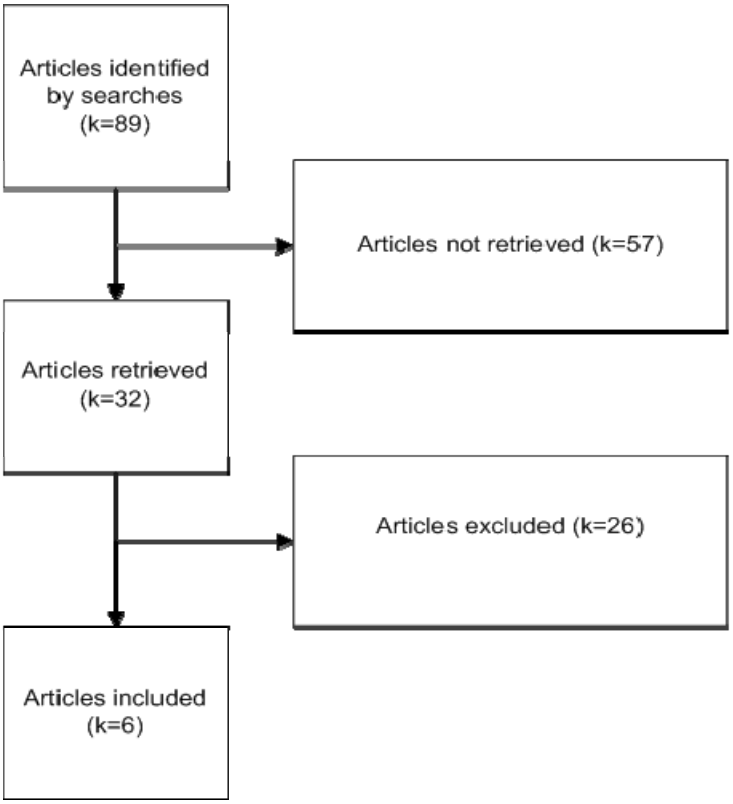
For this Key Question we thoroughly searched the medical literature to address the question of whether drivers who have had a stroke are at an increased risk of crash. We approached this in two ways. First, we searched for and analyzed direct evidence pertaining to the association between stroke and crash (Key Question 1: Part A). Second, we assessed the performance of drivers who have had a stroke on other measures of driving competence, specifically road and drivers licensure tests and driving simulation tests (Key Question 1: Part B).

Identification of Evidence Base

To meet the aims of this section of the evidence report, we searched for trials that compared crash risk or a surrogate outcome for crash risk (e.g., driver test, neuropsychological function) among individuals who have had a stroke and otherwise comparable individuals who have not had a stroke. Our search strategy is detailed in Appendix A. These searches identified 89 abstracts. Based upon our retrieval criteria (Appendix B), we retrieved 32 full length studies. Upon examination of the full-length articles, we found that 26 of those articles did not meet the inclusion criteria (Appendix C). These studies and the reason for their exclusion are listed in Table D-1 (Appendix D). The process used to develop the evidence base for Key Question 1 is

shown in Figure 9. A total of six studies, three of which directly assessed crash and three of which indirectly assessed crash risk by administering driving or driving simulation tests, were identified. Lists of included studies are provided in subsections A and B.

Figure 9. Development of Evidence Base for Key Question 1



Key Question 1 Part A: Direct Evidence—Stroke and Crash

Evidence Base

This subsection provides a brief description of the main attributes of the studies that comprise the evidence base for Key Question 1: Part A. Here we discuss information on the quality of the included studies and the generalizability of each study's findings to drivers of CMVs. The included studies are listed in Table 23.

Table 23. Evidence Base for Key Question 1 Part A: Direct Evidence

Reference	Year	Study Location	Country
McGwin et al.(136)	2000	Mobile County, AL	USA
Sims et al.(137)	2000	Jefferson County, AL	USA
Haselkorn et al.(138)	1998	Washington State	USA

Characteristics of Included Studies

Two case-control studies and one prospective cohort study were identified that met the inclusion criteria for Key Question 1 Part A. All three used police records to determine crash. However, the studies differed in how they determined whether drivers had strokes. Sims(137) and McGwin(136) relied on patient self-report, while Haselkorn et al.(138) used International Classification of Disease (ICD) codes. McGwin and Sims controlled for driving exposure using subject-reported estimated annual mileage, but Haselkorn et al. did not attempt to control for driving exposure. The primary characteristics of these studies are presented in Table 24.

Table 24. Key Study Design Characteristics of Studies that Address Key Question 1 Part A; Direct Evidence

Reference	Year	Design (prospective or retrospective)	Comparison	Definition of Stroke Used	Severity of Stroke	Driving Exposure Controlled for?	Primary Outcome	Outcome Self-reported?
McGwin et al.(136)	2000	Retrospective	Drivers without a history of stroke	Not reported, based on phone survey of included drivers	Not reported	Yes	Crash	No
Sims et al.(137)	2000	Prospective	Drivers without a history of stroke	Not reported, self-reported. Some patients have TIA*	Not reported.	Yes	Crash	No
Haselkorn et al.(138)	1998	Retrospective	Nonhospitalized drivers	ICD-9** codes	Not reported	No	Crash	No

* TIA: Transient Ischemic Attack
** ICD: International Classification of Disease
NR: Not reported

Quality of Included Studies

Using a revised version of the Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies and the Newcastle-Ottawa Quality Assessment Scale of Cohort Studies, we evaluated the quality (internal validity) of the included studies. As summarized in Table 25, no study was of high quality.

Table 25. Quality of the Studies that Assess Key Question 1 Part A: Direct Crash Evidence

Reference	Year	Quality Scale Used	Quality
McGwin et al.(136)	2000	Revised Newcastle-Ottawa Scale for Case-Control Studies	Moderate
Sims et al.(137)	2000	Revised Newcastle-Ottawa Scale for Cohort-Control Studies	Moderate
Haselkorn et al.(138)	1998	Revised Newcastle-Ottawa Scale for Case-Control Studies	Low

Observational studies, including case-control and cohort-control designs, are inherently susceptible to bias. Case-control studies are susceptible to potential biases resulting from retrospective assessment and imperfect case-control matching: because of these inherent flaws, case-control studies are never of high quality. Cohort design studies are susceptible to potential

biases resulting from differences in patient characteristics and measurement bias (particularly in how measurements are taken and how the data are analyzed), and, as with case-control studies, cannot be considered high quality.

All three of the included studies have the potential for measurement bias (specifically, the reports of disease state and risk exposure may not have been accurate), which may have influenced the study results. McGwin et al. and Sims et al. obtained disease status via individual telephone interviews of identified drivers who may not have given accurate information owing to reluctance to discuss health history or insufficient understanding of their health state. Hasselkorn et al. used ICD-9 codes to identify individuals who had had a stroke, but this type of assessment may not have identified all drivers with a history of stroke. In addition, studies may also have been affected by measurement bias in terms of risk exposure. Of particular import to studies that examine motor vehicle crash risk is the need to control or match for exposure to risk: examples of exposure to risk include the number of miles driven per unit time, the time frame over which data were collected, and the type(s) of roads used. McGwin et al. and Sims et al. attempted to control for risk exposure in terms of annual distance driven; however, both studies relied on self-reported estimated annual mileage, which may not be precise owing to the inaccuracy of individual recollections (recall bias). As no data on exposure were collected for Hasselkorn et al., it is possible that drivers with stroke drove much less than individuals without stroke, which could lead to an underestimation of crash risk compared with controls.

Generalizability of Evidence Base to Target Population

The purpose of this subsection is to provide details of the extent to which the individuals enrolled in the studies that address Key Question 1: Part A are similar to CMV drivers in the United States. Important details of the characteristics of the individuals enrolled in the studies that address Key Question 1 are presented in Table 26.

The generalizability of the findings of the included studies to CMV drivers is unclear. As stated earlier, no study examined crash risk specifically among individuals who held a current commercial driver's license. Exposure to risk is far lower among noncommercial vehicle drivers because noncommercial drivers drive fewer miles, on average, than CMV drivers. In addition, no study reported on the prevalence of comorbidity such as cardiovascular disease, which CMV drivers are likely to experience owing to their lifestyle. Also, women tend to be overrepresented in studies of crash risk among drivers with private motor vehicle driver licenses compared with the number of women in the CMV driver population. Finally, two of the three included publications studied only elderly drivers, who may be older on average than many CMV drivers.

Table 26. Generalizability of Studies that Address Key Question 1 Part A: Direct Evidence

Reference	Year	(Number of Individuals with stroke Included (n =)	Duration since stroke	% Male	% CMV Drivers	Mean Age (SD) in Years	Driving Exposure	% with Medically Restricted Licenses?	Generalizability to Target Population
McGwin et al.(136)	2000	51	NR	NR; of overall sample in crash 49.6%	NR	NR	NR, but adjusted for	NR	Unclear
Sims et al(137)	2000	17	NR	NR. Of entire sample 52.6% male	NR	NR. All 55+ years. Of entire sample 53.2% over 70 years	NR. For sample mean 7,900 miles per person per year.	NR	Unclear
Haselkorn et al.(138)	1998	1,910	Within 12 months	59.1%	NR	NR	NR	NR	Unclear

CMV Commercial motor vehicle.; NR Not reported.; SD Standard deviation.

Findings

As noted above, the evidence base for this Key Question is composed of two distinct types of studies. Haselkorn et al. compared crash risk among hospitalized individuals who had had a stroke and an otherwise comparable group of nonhospitalized individuals who did not have a stroke.(136) Sims et al. reported the crash rate per million miles driven of those with stroke compared with the rate of drivers without stroke. Outcome data from these studies were presented as an Incident Rate Ratio (RR). McGwin et al. compared the prevalence of stroke among individuals who were involved in a crash and a comparable group of individuals who were not.(136) Outcome data from this study were presented as the Odds Ratio (OR). Although both types of study may be considered to address the same question from a qualitative perspective ("Does stroke represent an increased crash risk?"), they differ significantly from a quantitative perspective, which is why different metrics are required to assess them.

Crash Risk among drivers who have had a stroke compared to drivers who have not had a stroke

Two of the three studies assessed this outcome, with conflicting findings. Haselkorn et al. did not provide evidence that individuals with stroke are at an increased risk for a motor vehicle crash, including when adjusted for age, gender, and number of crashes and traffic citations during the year prior to stroke. However, the findings of Sims et al., adjusted for age, gender, race, and days of driving per week and reported in terms of miles driven, suggest that drivers who have had a stroke do have an increased risk of crash (Table 27).

Table 27. Crash Risk in Drivers with Stroke Compared to Drivers without Stroke

Reference	Year	Units	Crash Rate Data				Evidence of Increased Crash Risk
			Crash Rate (cases)	Crash Rate (rest of population)	Rate Ratio* (95% CI)	*P* =	
Sims et al.(137)	2000	Crashes per million miles driven	21.1	10.0	2.71 (1.11–6.61)	0.03	Yes
Haselkorn et al.(138)	1998	Proportion of drivers with stroke who crashed to proportion of drivers without stroke who crashed per person year	2.6 (50/1,910)	3.1 (116/3,732	0.8 (0.6–1.2)	0.303*	No

* Calculated by ECRI Institute from reported data. Effect size estimates >0.05 indicate that individuals with stroke are at increased risk for a motor vehicle accident when compared with individuals without the disorder. Negative effect sizes show they are at decreased risk.

Prevalence of stroke among drivers who crashed

One study, McGwin et al., assessed the crash risk associated with stroke among the general driver population as an OR study.(139) This study did not show evidence of a raw increased crash risk. However, when adjusted for age, race, and annual mileage, the increased risk of crash is significant. Findings from McGwin et al. are shown in Table 28.

Table 28. Findings of Odds Ratio Studies

Reference	Year	Units	Crash Rate Data				Evidence of Increased Crash Risk
			At-fault in crash	Not in crash	Odds Ratio* (95% CI)	*P* =*	
McGwin et a.(140)	2000	Proportion of at-fault drivers involved in crashes who have history of stroke to proportion drivers not involved in crashes with history of stroke	7.3% (18/249)	4.1% (19/454)	1.8 (0.9-3.7) Unadjusted	0.088	Yes
					1.9 (1.0-3.9) Adjusted†	‡	

* Calculated by ECRI Institute from reported data.
† Adjusted for age, race, and annual mileage.
‡ No *P*-value available because not reported by study authors and data on adjustment of odds ratio were not reported; ECRI Institute could not calculate from reported effect size because 95 percent CI not symmetric.

Key Question 1 Part B: Indirect Evidence—Stroke and Driving Simulation and On-road Tests

In addition to directly assessing the risk for crash, we searched for comparative trials that assessed the association between stroke and other measures of driving performance, such as driving tests and simulation. Driving tests and simulator tests do not provide perfect information on how likely a driver is to crash, however, they still offer meaningful information about driver safety. (See Table 29)

Evidence Base

This subsection provides a brief description of the main attributes of the studies that comprise the evidence base for Key Question 1 Part B. Here we discuss information on the quality of the included studies, and the generalizability of each study's findings to drivers of CMVs.

Table 29. Evidence Base for Key Question 1 Part B: Indirect Driving Evidence

Reference	Year	Study Location	Country
Lings and Jensen(141)	1991	Aarhus	Denmark
Lundqvist et al.(142)	2000	Linkoping	Sweden
Wilson and Smith(143)	1983	Bedfordshire	UK

Characteristics of Included Studies

The primary characteristics of the included studies that address Key Question 1 Part B are presented in Table 30. All identified studies are prospective cohort control studies that compare performance on driving tests or driving simulation between individuals who have had a stroke and individuals who have not. The severity of stroke experienced was typically not well characterized.

Table 30. Key Study Design Characteristics of Studies that Address Key Question 1 Part B: Indirect Driving Evidence

Reference	Year	Severity of Stroke	Severity Level Definition	Prospective or Retrospective	Study Design Type	Comparison
Lings and Jensen(141)	1991	NR; all patients have hemiparesis	NR	Prospective	Cohort Control	Drivers without history of stroke
Lundqvist et al.(142)	2000	NR	NR	Prospective	Cohort Control	Drivers without history of stroke
Wilson and Smith(143)	1983	NR	NR	Prospective	Cohort Control	Drivers without history of stroke

Quality Assessment

We assessed the quality of each of the studies using the Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies. Because these studies used a cohort design, they are susceptible to potential biases resulting from differences in patient characteristics, and measurement bias (particularly in how measurements are taken and how the data are analyzed). For these reasons, cohort-control studies cannot be considered high in quality. The findings of our assessment are summarized in Table 31. All studies were rated low in quality.

Table 31. Quality of the Studies that Assess Key Question 1 Part B: Indirect Driving Evidence

Reference	Year	Quality Scale Used	Quality Category
Lings and Jensen(141)	1991	Revised Newcastle-Ottawa Quality Scale for Cohort Studies	Low
Lundqvist et al.(142)	2000	Revised Newcastle-Ottawa Quality Scale for Cohort Studies	Low

Reference	Year	Quality Scale Used	Quality Category
Wilson and Smith(143)	1983	Revised Newcastle-Ottawa Quality Scale for Cohort Studies	Low

Generalizability of Evidence Base to Target Population

The purpose of this subsection is to provide details of the extent to which the individuals enrolled in the studies that address Key Question 1 Part B are similar to CMV drivers in the United States. Important characteristics of the individuals included in the studies that address Key Question 1 Part B are presented in Table 32.

The generalizability of the findings of the studies included in this section of the report to CMV drivers is unclear. Most important, none of the studies sought out CMV drivers for inclusion, and none of the studies report that CMV drivers were enrolled. Mean miles driven per year and proportion of drivers with medically restricted licenses were not reported by any study. Of the two studies that reported on gender, the proportions of male drivers were 70 percent and 81 percent. Although men are clearly in the majority, women may be overrepresented in the populations compared with CMV driver populations. The duration since stroke and severity of stroke and related signs and symptoms were generally not clearly defined.

Table 32. Generalizability of Studies that Address Key Question 1 Part B: Indirect Driving Evidence

Reference	Year	(Number of Individuals with stroke Included (n =)	Duration since stroke	% Male	% CMV Drivers	Mean Age (SD) in Years	Driving Exposure	% with Medically Restricted Licenses?	Generalizability to Target Population
Lings and Jensen(141)	1991	11	NR; "some months"	NR	NR	NR	NR	NR	Unclear
Lundqvist et al.(142)	2000	30	Mean 8.6 months	70%	NR	68 (4.3) years	NR	NR	Unclear
Wilson and Smith(143)	1983	46	1 month – 18 years, median 2 years	81%	NR	Median 58, range 24-78	NR	NR	Unclear

CMV Commercial motor vehicle.; NR Not reported.; SD Standard deviation.

Findings

Two studies reported results from on-road driving tests, and two reported results from a driving simulator test (one study reported both simulator and road test outcomes). Of the two studies that used driving simulators, one found that stroke drivers were impaired compared with controls, while the other did not. However, of the two studies that conducted on-road testing, both found that drivers who had a stroke performed significantly more poorly than drivers without a history of stroke on many measures. Owing to the differences in testing methods and outcomes assessed

among the three studies, their findings cannot be quantitatively combined. Therefore, we discuss the findings of each study separately below.

Study of Lings and Jensen 1991(141)

Lings and Jensen studied the driving ability of 113 individuals who had suffered a stroke that resulted in hemiparesis and 109 individuals with no history of stroke, using a driving simulator. Of the individuals who had suffered a stroke, 46 had left-sided hemiparesis and 67 had right-sided hemiparesis. In 17 stroke survivors, driving ability was so compromised that the driving simulation could not be completed.

The authors analyzed the right- and left-side hemiparesis groups separately. For both groups, reaction time was a covariate with degree of paresis. Drivers who had a stroke were also more likely not to complete the test in the allotted time and to have to be urged to complete the test. Differences between the left-sided group and controls on total number of errors, skills in turning, braking, and driving in the correct direction were not statistically significant. In the right-sided group, the drivers who had had a stroke had a significantly greater number of total errors, significantly more directional errors, were significantly more likely to commit two or more errors than controls. Significantly greater proportions of drivers with left-sided paresis had two or more errors or failed to react one or more times.

The authors concluded that there was an important relationship between degree of paresis and secondary reaction times. They found that left-sided hemiparesis was associated with poorer steering wheel reaction time. Drivers with right-sided hemiparesis had more directional errors. Overall, drivers who had a stroke experienced more driving-related deficits than drivers who had not had a stroke.

Study of Lundqvist et al. 2000(142)

Lundqvist et al. enrolled 30 drivers who had suffered a stroke and 30 drivers who had not and tested their performance on both driving simulation and an actual road test. Ten additional drivers with stroke had been recruited but were subsequently excluded because they were physically unable to adequately operate the adapted car used in the simulation test. Controls were matched to the drivers with stroke by age, gender, education level, years of driving, and the annual driving mileage of individuals before their stroke.

On the driving simulation test, there were no significant differences between the 23 patients who had suffered a stroke and the 29 controls, with one exception. Controls scored better on the Listening Span test, which involves processing and recalling words while driving.

Differences between groups were pronounced in the on-road driving test. Controls scored significantly better on speed, maneuvering, lateral position, and traffic behavior. A substantially greater proportion of post-stroke drivers (14/28, 50 percent) were classified with “low driving skill,” compared with controls (6/30, 20 percent). Eight post-stroke patients did not resume

driving after their stroke; these patients did not score significantly different from post-stroke patients who continued driving on the simulation or road test.

Study of Wilson and Smith 1983(143)

Wilson and Smith enrolled 11 patients who had suffered a stroke and 11 controls who had not had a stroke for an on-road driving study. Controls were selected from the community and from hospital employees. Half were young adults, aged 18-26. The controls were not matched with cases. All drivers were assessed by two evaluators who were both passengers during the driving test; inter-rater reliability approached perfect.

The drivers who had suffered a stroke performed significantly worse than drivers who had not had a stroke on tasks including signaling and use of mirror when merging onto a freeway, merging into the correct lane, correct exit from freeway, slow and careful driving where appropriate, awareness, response to emergency, and proper right-hand turn with full stop and signaling. Driving environments included driving on the highway and driving on private roads.

Study authors concluded that drivers who had suffered a stroke had particular difficulty entering and leaving a freeway, driving in traffic circles, and responding to emergency on a private road. The authors also observed that some drivers had trouble with tasks that involved complex reversing and placing the car on the left (study conducted in UK).

Section Summary

Evidence suggests that drivers who have suffered a stroke are at an increased risk of crash (Strength of Conclusion: Minimally Acceptable). The precise magnitude of this increased risk could not be determined.

Direct Evidence—Crash Studies*: Current direct evidence from two of three crash studies found that individuals who have had a stroke are at an increased risk for a crash. The two studies that detected an increased risk of crash adjusted for miles driven, while the study that did not find an increased risk of crash did not perform this adjustment. As risk exposure is the most important factor in determining risk, the findings of the two studies that adjusted for risk exposure should be given stronger consideration than the study that did not. The increased risk could not be quantified owing to differences in reporting. Limitations of the evidence supporting this conclusion are the small size of the evidence base (three studies) and overall low- to moderate-quality.*

Indirect Evidence—Studies of Driving Tests and Driving Simulation: *Two studies of on-road driving tests provide consistent, albeit weak evidence that suggests that individuals who have suffered stroke may be at increased risk for a motor vehicle crash owing to their poor driving skills. Findings from two simulator studies are conflicting. However, the findings of the direct crash and on-road driving tests should supersede simulator test findings because they provide more relevant information on crash risk than simulator studies. Limitations of the evidence base include weakness of type of evidence (since it is indirect), small size of the evidence base, and*

overall low quality. In particular, controls may not have been well suited to drivers who had a stroke.

Key Question 2: Can neuropsychological testing of individuals who have experienced a stroke predict crash risk?

Introduction

Because of the paucity of data on incidence of crash in stroke survivors, identifying reliable surrogate outcomes is desirable to determineg whether stroke survivors have an increased risk of crash. Neuropsychological tests are often used to determine the degree of impairment in stroke survivors. These tests evaluate patients in domains including attention and concentration, visuospatial skills, and executive function, which are potentially relevant to the safe operation of a motor vehicle. Authors of a systematic review of 17 studies concluded that neuropsychological tests are associated with fitness to drive, as determined by driving tests, off-road evaluation, and driving cessation.(144) However, the actual relationship between neuropsychological test results and crash risk is unknown.

Identification of Evidence Base

To meet the aims of this section of the evidence report, we searched for trials that studied the relationship between neuropsychological test findings and crash incidence or driving performance. Our search strategy is detailed in Appendix A. These searches identified 20 abstracts. Based on our retrieval criteria (Appendix B), we retrieved 17 full- length studies. Upon examination of the full-length articles, we found that 12 met our inclusion criteria (Table 33). The studies excluded from the evidence base are listed in Table D-1 (Appendix D).The process used to develop the evidence base for Key Question 2 is shown in Figure 10.

Figure 10. Development of Evidence Base for Key Question 2

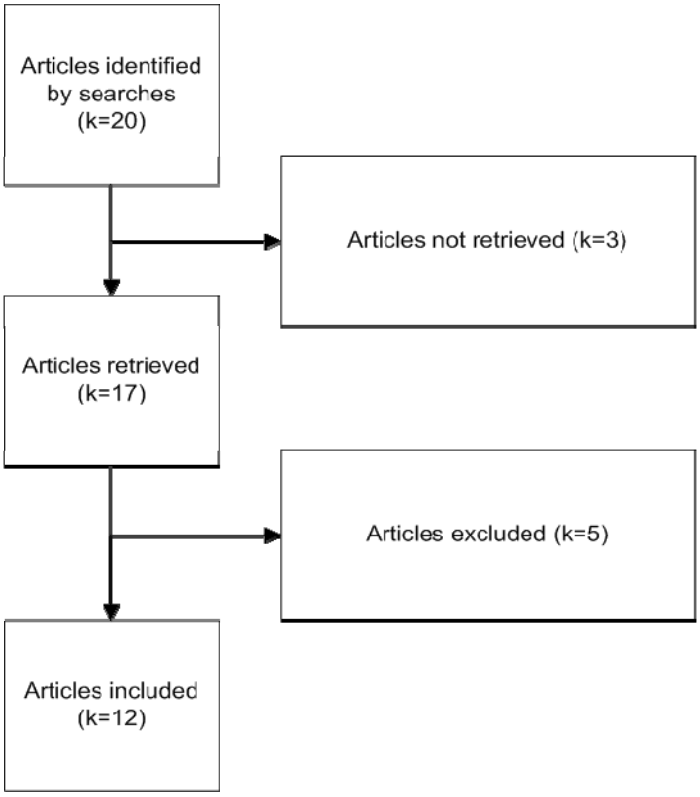


Table 33. Evidence Base for Key Question 2

Reference	Year	Study Location	Country
Akinwuntan et al.(145)	2006	Brussels	Belgium
Bouillon et al.(146)	2006	Laval, Quebec	Canada
Smith-Arena et al.(147)	2006	White Plains, New York State	USA
Soderstrom et al.(99)	2006	Vasteras	Sweden
Lundberg et al.(148)	2003	Stockholm	Sweden
Akinwuntan et al.(149)	2002	Brussels	Belgium
Korner-Bitensky et al.(150)	2000	Laval, Quebec; Montreal, Quebec; Hull, Quebec Poughkeepsie, New York; Fort Wayne, Indiana; Madison, Wisconsin	Canada and USA
Lundqvist et al.(142)	2000	Linkoping	Sweden
Mazer et al.(151)	1998	Montreal	Canada
Nouri and Lincoln(152)	1993	Mansfield, Lincoln, Nottingham	United Kingdom
Nouri and Lincoln(153)	1992	Nottingham	United Kingdom

Reference	Year	Study Location	Country
Nouri et al.(154)	1987	Nottingham	United Kingdom

Evidence Base

This subsection provides a brief description of the key attributes of the 12 studies that comprise the evidence base for Key Question 2. Here we discuss applicable information on the quality of the included studies and the generalizability of each study's findings to drivers of CMVs.

Characteristics of Included Studies

The primary characteristics of the 12 included studies that address Key Question 2 are presented in Table 34. The majority were cohort studies that evaluated the ability of various neuropsychological tests to predict the outcome of an on-road test or driver evaluation. Neuropsychological test scores of stroke patients who passed their road test were compared with the test scores of patients who failed their road test to determine if the scores differed significantly. Most studies used several different neuropsychological tests, and although there was overlap in the use of some tests among these studies, no two studies used an identical array of tests. One randomized controlled trial (RCT) compared neuropsychological testing with general physician assessment in terms of relative ability to predict road test outcomes. Eight of the twelve studies had a prospective design; the remaining four were retrospective. Only one study provided information on the severity of stroke among their study population.

Table 34. Key Study Design Characteristics of Studies that Address Key Question 2

Reference	Year	Severity of Stroke	Neuropsychological Tests Used in Study	Prospective or Retrospective	Study Design	Comparison
Akinwuntan et al.(145)	2006	NR	Figure of Rey, Useful Field of View (UFOV) and Test for Attentional Performance (TAP), component tests of the Stroke Driver Screening Assessment (SDSA), which includes dot cancellation test, square matrix tests, and the road sign recognition test	Prospective	Cohort	Comparison based on outcome of fitness to drive assessment (fit, temporarily unfit, or unfit) and also outcome of on-road test.
Bouillon et al.(146)	2006	NR	Motor-Free Visual Perception Test (MVPT), Cognitive Behavioral Driver's Inventory (CBDI), which includes Wechsler Adult Intelligence Scale – Revised Picture Completion and Digit Symbol subtests; Trail Making Test, Parts A and B; brake reaction test, examination of visual fields, and four components of Bracy's Computer Assisted Cognitive Rehabilitation	Retrospective	Cohort	Comparison based on outcome of on-road driving evaluation (pass vs. fail)

Reference	Year	Severity of Stroke	Neuropsychological Tests Used in Study	Prospective or Retrospective	Study Design	Comparison
Smith-Arena et al.(147)	2006	MMSE (mean ± SD): 22.7 ± 8.1 Visual field: Normal: 32(82%) Left hemianopsia: 3 (7.6%) Right hemianopsia: 2 (5.1%) Left visual neglect: 2 (5.1%) Right visual neglect: 0 Upper Limb Motricity Index: 63.7 ± 34.8 Lower Limb Motricity Index: 71.8 ± 24.3 Limb Placement Task: 4.6 ± 6	Mini-Mental State Examination (MMSE)	Prospective	Cohort	Comparison based on outcome of in-clinic driver evaluation (pass vs. fail)
Soderstrom et al.(99)	2006	NR	Trail Making Test Part B, the Wisconsin Card Sorting Test, the Rey Complex Figure Test, the Digit-Symbol Test, and two components from the Automated Psychological Tests (APT): the Reaction Time Test and the Finger Tapping Test	Prospective	Cohort control	Comparison based on outcome of on-road driving evaluation (pass vs. fail) Also compared neuropsychological test results and driving test results of stroke patients and healthy controls
Lundberg et al.(148)	2003	NR	Stroke Driver Screening Assessment (SDSA), which includes the dot cancellation test, the directions test, the compass test, and the road Sign recognition test	Prospective	Cohort	Comparison based on outcome of road test (pass, borderline pass, and fail)
Akinwuntan et al.(149)	2002	NR	Figure of Rey, UFOV, and six tests from the Fimm-Zimmermann test battery (divided attention, flexibility, visual scanning, incompatibility, visual field, and neglect)	Retrospective	Cohort	Comparison based on outcome of road test
Korner-Bitensky et al.(150)	2000	NR	MVPT	Retrospective	Cohort	Comparison based on outcome of on-road driving evaluation (pass vs. fail)
Lundqvist et al.(142)	2000	NR	Trail Making Test B, Digit Symbol, the Color Word Test, Paced Auditory Serial Addition Test (PASAT), modified Listening Span test; Automated Psychological Tests (APT), including the Finger Tapping test, K test, Reaction Time test, and Simultaneous Capacity test; Wisconsin Card Sorting Test (WCST)	Prospective	Cohort control	Comparison based on outcome of on-road driving test (high skill vs. low skill) Also compared neuropsychological test results and driving test results between stroke patients and healthy controls
Mazer et al.(151)	1998	NR	MVPT, Trail Making Test Parts A and B, the Complex Reaction Timer, the Single Letter Cancellation Test, the Double Letter Cancellation Test, the Money Road Map Test of Direction Sense, the Bells Test, and the Charron Test	Retrospective	Cohort	Comparison based on outcome of on-road driving evaluation (pass vs. fail)

Reference	Year	Severity of Stroke	Neuropsychological Tests Used in Study	Prospective or Retrospective	Study Design	Comparison
Nouri and Lincoln(152)	1993	NR	SDSA	Prospective	RCT	Comparison based on outcome of road test (pass vs. fail) Also comparison of neuropsychological tests and general physician assessment as predictors of road test outcome
Nouri and Lincoln(153)	1992	NR	Cube Copy test, dot cancellation test, Rey Figure Copy and Recall, What's in the Square, What Else is in the Square, Pursuit Rotor, Token Test Part V, Titmus Vision Tester and Perimeter, Road Sign Recognition test, Recognition Memory test – Faces, and Hazard Recognition Task	Prospective	Cohort	Comparison based on outcome of road test (pass vs. fail)
Nouri et al.(154)	1987	NR	Cube Copy test, dot cancellation test, Rey Figure Copy and Recall, Four Choice Reaction Time, What's in the Square, What Else is in the Square, Pursuit Rotor, Token Test Part V, Titmus Vision Tester and Perimeter, Road Sign Recognition Test, Hand Sequencing Task, Recognition Memory Test – Faces, and Hazard Recognition Task	Prospective	Cohort	Comparison based on outcome of road test (pass, borderline, or fail)

Quality of Evidence Base

The findings of our assessment of the quality of the studies that comprise the evidence base for Key Question 2 are summarized in Table 35. Complete details of our quality assessment can be found in the Quality Score Tables in Appendix G. All studies were rated using a revised version of the Newcastle-Ottawa quality assessment scale for cohort studies.

The majority of included studies were rated as being of moderate quality, with only one study scoring as low quality. The quality of cohort studies is limited because of their inability to control for unknown confounding factors, which is possible only through random allocation. They are also susceptible to measurement bias (particularly in how measurements are taken and how the data are analyzed). One study by Nouri and Lincoln (1993)(152) was technically an RCT comparing neurocognitive testing as a predictor of road test performance to physician assessment without neurocognitive testing as a predictor of road test performance. For the purposes of our analysis, we only evaluated the group that underwent neurocognitive testing, so the study was basically analyzed as a cohort study.

Table 35. Quality of the Studies that Assess Key Question 2

Reference	Year	Quality Scale Used	Quality
Akinwuntan et al.(145)	2006	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Bouillon et al.(146)	2006	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate

Reference	Year	Quality Scale Used	Quality
Smith-Arena et al.(147)	2006	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Low
Soderstrom et al.(99)	2006	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Lundberg et al.(148)	2003	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Akinwuntan et al.(149)	2002	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Korner-Bitensky et al.(150)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Lundqvist et al.(142)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Mazer et al.(151)	1998	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Nouri and Lincoln(152)	1993	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Nouri and Lincoln(153)	1992	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Nouri et al.(154)	1987	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate

Generalizability of Evidence to Target Population

Our assessment of the generalizability of the findings of the studies that form the evidence base for Key Question 3 is based on the characteristics of the individuals enrolled in each of the included studies. These characteristics are presented in Table 36. The mean age of enrolled subjects (where reported) ranged from 53 to 68 years, which may be older than the mean age of CMV drivers. The proportion of males enrolled in the studies ranged from 70 percent to 94 percent, indicating that these studies tended to have a greater proportion of women than the CMV driver population. None of the studies reported whether any of the enrolled patients were CMV drivers (although one study reported that 38 percent of enrollees were "professional" drivers, which would presumably include some CMV drivers). Thus, the generalizability of the findings of these studies to the CMV driver population remains unclear.

Table 36. Generalizability of Studies that Addressed Key Question 2

Reference	Year	Number of Individuals with stroke (n =)	Duration since stroke	% Male	Mean Age (SD) in Years	Ethnicity	% CMV Drivers	Generalizability to Target Population
Akinwuntan et al.(145)	2006	68	15 ± 18 months	83.8	53 ± 13	NR	NR	Unclear
Bouillon et al.(146)	2006	48/172	NR	Whole group: 78.5	Whole group: 58.9 ± 17.9	NR	NR	Unclear
Smith-Arena et al.(147)	2006	39	10.4 ± 11.3 days	74.4	71 ± 9.8	NR	NR	Unclear
Soderstrom et al.(99)	2006	34	Median 6.2 months (range 1.4 to 14 months)	94	54 ± 8.8	NR	38.2 ("professional" drivers)	Unclear
Lundberg et al.(148)	2003	97	1.1 ± 1.5 years	89.7	63 ± 12.5	NR	NR	Unclear
Akinwuntan et al.(149)	2002	104	18.5 ± 20 months	78.8	56.8 ± 11.9	NR	NR	Unclear
Korner-Bitensky et al.(150)	2000	269	6.9 ± 11 months	80	63.6 ± 12.5	NR	NR	Unclear

Reference	Year	Number of Individuals with stroke (n =)	Duration since stroke	% Male	Mean Age (SD) in Years	Ethnicity	% CMV Drivers	Generalizability to Target Population
Lundqvist et al.(142)	2000	30	8.6 months (range 3-14 months)	70	68.3 ± 4.8	NR	NR	Unclear
Mazer et al.(151)	1998	84	10.4 ± 15.8 months	75	60.8 ± 11.9	NR	NR	Unclear
Nouri and Lincoln(152)	1993	27	Mean: 44.4 weeks	85.2	58.8	NR	NR	Unclear
Nouri and Lincoln(153)	1992	40	33.1 ± 40.7 weeks	90	61.1 ± 14.1	NR	NR	Unclear
Nouri et al.(154)	1987	39	6 weeks to 4 years	92.3	59 ± 10	NR	NR	Unclear

NR–Not reported.

Findings

The 12 included studies examined the value of neuropsychological tests for predicting the outcome of road tests or in-clinic driving assessments; in most studies, the outcome was pass or fail. All of these studies identified significant predictors of outcome using either multiple regression models or discriminant function analysis. These techniques are superior to simple univariate comparisons because they statistically adjust for the effects of other variables in the model; thus, the identified correlations represent the true association of the predictor variable and the outcome.

Eleven of 12 studies found that one or more neuropsychological tests were significant predictors of the outcome of road tests or driving evaluations for patients who had experienced a stroke. These findings could not be combined in a quantitative analysis because no two studies used the same array of tests or evaluated the same combination of variables when attempting to identify predictors of outcome. However, certain tests were found to be significant outcome predictors in multiple studies. Figure of Rey was identified as a significant outcome predictor in three out of five studies that used it.(145,149,154) The dot cancellation test, part of the Stroke Driver Screening Assessment (SDSA), was found to be a significant outcome predictor in four out of four studies.(145,148,153,154) Another SDSA test (the Road Sign Recognition test) was found to be a significant outcome predictor in two out of four studies.(148,153) A third SDSA test (What Else is in the Square) was a significant outcome predictor in two out of three studies.(153,154) Two out of three studies that used the Motor-Free Visual Perception Test (MVPT) identified it as a significant outcome predictor.(150,151) Other tests identified as significant outcome predictors in only one study included the Cognitive Behavioral Driver's Inventory (CBDI, a compendium of several tests), the Trail-Making Test Part B, the Mini-Mental State Examination (MMSE), the Complex Reaction Time test, the Compass Test, the Pursuit Rotor test, the Recognition Memory test, the Square Matrix (Compass) Test, and the Hazard Recognition test.(142,146-148,154) Given the moderate quality of the studies and the consistency of the findings for

neuropsychological tests overall, the strength of evidence supporting the ability of these tests to predict driving test outcomes is moderate.(Table 37)

However, none of these studies evaluated the relationship between neuropsychological test results and actual crash risk as measured by crash data. Prediction of driving test outcomes is not the same as prediction of crash risk. Patients who failed road tests or in-clinic driving assessments would either not be allowed to drive or at least advised not to drive, depending on the laws of the particular state or country of residence. Thus, they would not be expected to be at risk for motor vehicle crash (unless they disregard laws or advice). Whether neuropsychological testing can identify stroke patients at increased risk of crash who were able to pass a road test has not been evaluated in the currently available literature.

Table 37. Results of Studies Evaluating Neuropsychological Tests as Predictors of Driving Assessment Outcomes

Reference	Year	Comparison	Neuropsychological tests used in study	Results
Akinwuntan et al.(145)	2006	Comparison based on outcome of fitness to drive assessment (fit, temporarily unfit, or unfit) Also compared outcome of on-road test	Figure of Rey, Useful Field of View (UFOV) and Test for Attentional Performance (TAP), component tests of the Stroke Driver Screening Assessment (SDSA), which includes dot cancellation test, square matrix tests, and the road sign recognition test	Variables that best predicted outcome of fitness to drive assessment in multiple regression model. **Variable** **β** **p-value** **0dds Ratio** Visual neglect -0.01 0.005 0.99 Figure of Rey 0.36 0.02 1.43 On-road test 0.06 0.0001 1.06 This model explained 73% of the variance. Variables that best predicted outcome of on-road test. **Variable** (effect sizes and p-values not reported) Binocular acuity Dot cancellation test Square matrix (compass) Incompatibility test This model explained 35% of the variance.
Bouillon et al.(146)	2006	Comparison based on outcome of on-road driving evaluation (pass vs. fail)	Motor-Free Visual Perception Test (MVPT), Cognitive Behavioral Driver's Inventory (CBDI), which includes Wechsler Adult Intelligence Scale – Revised Picture Completion and Digit Symbol subtests; Trail-Making Test, Parts A and B; brake reaction test, examination of visual fields, and four components of Bracy's Computer Assisted Cognitive Rehabilitation	Variables that best predicted outcome of on-road driving evaluation in logistic regression model. Left CVA **Variable** **β** **p-value** **Odds Ratio (95% CI)** Time since diagnosis -0.48 0.02 0.62 (0.42-0.91) Right CVA **Variable** **β** **p-value** **Odds Ratio (95% CI)** CBDI -0.61 0.03 0.54 (0.32-0.93)
Smith-Arena et al.(147)	2006	Comparison based on outcome of in-clinic driver evaluation (pass vs. fail)	Mini-Mental State Examination (MMSE)	Variables that best predicted outcome of fitness to drive assessment in logistic regression model. **Variable** **β** **p-value** **0dds Ratio (95% CI)** MMSE 0.112 0.041 1.119 (1.004-1.246) MMSE explained 74% of the variance.

Reference	Year	Comparison	Neuropsychological tests used in study	Results
Soderstrom et al.(99)	2006	Comparison based on outcome of on-road driving evaluation (pass vs. fail) Also compared neuropsychological test results and driving test results between stroke patients and healthy controls	Trail-Making Test Part B, The Wisconsin Card Sorting test, The Rey Complex Figure test, The Digit-Symbol test, and two components from the Automated Psychological Tests (APT): the Reaction Time test and the Finger Tapping test	Variables that best predicted outcome of road test in multiple regression model. **Variable** **Pearson's r** **p-value** Age -0.402 0.018 None of the neuropsychological tests showed a significant correlation with road test outcome (pass/fail).
Lundberg et al.(148)	2003	Comparison based on outcome of road test (pass, borderline pass, and fail)	Stroke Driver Screening Assessment (SDSA), which includes the dot cancellation test, the directions test, the compass test, and the road sign recognition test	Variables found to predict outcome of road test in discriminant function analysis. Equations: PASS (Dot cancellation, time in seconds x 0.0298) + (Dot cancellation, misses x 0.1017) + (Compass x 0.3666) + (Road sign recognition x 1.0415) -16.7757 (Constant). FAIL (Dot cancellation, time in seconds x 0.0294) + (Dot cancellation, misses x 0.1563) + (Compass x 0.2607) + (Road sign recognition x 0.8780) -15.1846 (Constant). These formulas correctly classified outcomes in 78% of cases.
Akinwuntan et al.(149)	2002	Comparison based on outcome of road test Comparison based on final group decision on driving fitness	Figure of Rey, UFOV, and six tests from the Fimm-Zimmermann test battery (divided attention, flexibility, visual scanning, incompatibility, visual field, and neglect)	Variables that best predicted outcome of road test in multiple regression model. **Variable** **Parameter estimate** **p-value** Acuity of left and right eye 2.84 0.003 Figure of Rey 1.19 0.0002 This model, although the most predictive, only accounted for 28% of the variance. Variables that best predicted outcome of final group decision in multiple regression model. **Variable** **Parameter estimate** **p-value** Side of lesion -1.23 0.02 Kinetic vision 0.81 0.01 Scanning -0.16 0.04 Road test (5 units) -0.14 <0.001 This model accounted for 53% of the variance.
Korner-Bitensky et al.(150)	2000	Comparison based on outcome of on-road driving evaluation (pass vs. fail)	MVPT	Variables that best predicted outcome of road test in multiple regression model. **Variable** **Parameter estimate** **p-value** Age NR NR MVPT score NR NR Although numbers not reported, "the greatest odds of failing were predicted by the model including age and MVPT score". Lower MVPT score and older age were associated with failing the road test.

Reference	Year	Comparison	Neuropsychological tests used in study	Results
Lundqvist et al.(142)	2000	Comparison based on outcome of on-road driving test (high skill vs. low skill) Also compared neuropsychological test results and driving test results between stroke patients and healthy controls	Trail-Making Test B, Digit Symbol, the Color Word test, Paced Auditory Serial Addition Test (PASAT), modified Listening Span test; Automated Psychological Tests (APT), including the Finger Tapping test, K test, Reaction Time test (Simple and Complex), and Simultaneous Capacity test; Wisconsin Card Sorting Test (WCST)	Variables that best predicted outcome of road test in multiple regression model. **Variable** — **Chi-square** — **p-value** Complex Reaction Time — 15.76 — <0.01 Factor 3 (Cognitive processing) — 3.08 — <0.01 Factor 3 (cognitive processing) is a combination of scores on PASAT, the Color Word Test, the Listening Span test, and the K test, identified through factor analysis. This model classified 83% of the subjects correctly with respect to driving test outcome.
Mazer et al.(151)	1998	Comparison based on outcome of on-road driving evaluation (pass vs. fail)	MVPT, Trai-Making Test Parts A and B, the Complex Reaction Timer, the Single Letter Cancellation test, the Double Letter Cancellation test, The Money Road Map Test of Direction Sense, the Bells test, and the Charron test	Variables that best predicted outcome of road test in logistic regression models. All patients **Variable** — **Coefficient** — **0dds Ratio (95% CI)** MVPT (≤30, >30) — 1.85 — 6.36 (2.04-19.82) Trail Making B (<3, ≥3) — 1.26 — 3.53 (0.99-12.60) Left CVA **Variable** — **Coefficient** — **0dds Ratio (95% CI)** Trail Making B (<3, ≥3) — 2.44 — 11.47 (2.17-60.70) Right CVA **Variable** — **Coefficient** — **0dds Ratio (95% CI)** MVPT (≤30, >30) — 1.85 — 15.03 (1.67-134.99)
Nouri and Lincoln(152)	1993	Comparison based on outcome of road test (pass vs. fail) Also a comparison of neuropsychological tests and general physician assessment as predictors of road test outcome	SDSA	SDSA predicted road performance of 81% of patients, whereas general physician assessment predicted performance of 56% of patients. SDSA likelihood ratio = 6.0 (1.5 to 24.0) Physician assessment likelihood ratio = 2.0 (0.3 to 12.0)
Nouri and Lincoln(153)	1992	Comparison based on outcome of road test (pass vs. fail)	Cube Copy test, dot cancellation test, Rey Figure Copy and Recall, What's in the Square, What Else is in the Square, Pursuit Rotor, Token Test Part V, Titmus Vision Tester and Perimeter, Road Sign Recognition test, Recognition Memory Test – Faces, and Hazard Recognition Task	Variables found to predict outcome of road test in discriminant function analysis. Equations: PASS (Dot cancellation – time in seconds x 0.012) + (Dot cancellation – false positives x 0.216) + (What Else is in the Square x 0.409) + (Road sign recognition x 1.168) -13.79. FAIL (Dot cancellation – time in seconds x 0.017) + (Dot cancellation – false positives x 0.035) + (What Else is in the Square x 0.185) + (Road sign recognition x 0.813) -10.042. These formulas correctly classified outcomes in 82% of cases.
Nouri et al.(154)	1987	Comparison based on outcome of road test (pass, borderline, or fail)	Cube Copy test, dot cancellation test, Rey Figure Copy and Recall, Four Choice Reaction Time, What's in the Square, What Else is in the Square, Pursuit Rotor, Token Test Part V, Titmus Vision Tester and Perimeter, Road Sign Recognition Test, Hand Sequencing Task, Recognition Memory Test – Faces, and Hazard Recognition Task	Variables found to predict outcome of road test in discriminant function analysis. Equation: (Dot cancellation – false positives x 0.14) + (Rey Figure Copy x -0.10) + (What Else is in the Square x 0.09) + (Pursuit Rotor – 15 rpm x 0.05) + (Token Test x -0.12) + (Visual Acuity – near x 0.19) + (Visual field – left x 0.03) + (Recognition Memory Test – faces x -0.19) + (Cube Copy x 0.09) + (Hazard Recognition x 0.12) + -1.19 This formula correctly classified outcome of 94% of cases.

Section Summary

Certain neuropsychological tests may predict the outcome of driving performance measured by a road test or in-clinic driving evaluation (Strength of Conclusion: Moderate). Whether neuropsychological tests can predict actual crash risk cannot be determined from currently available evidence.

No studies provided direct evidence of an association between neuropsychological test results and crash risk. The only available indirect evidence evaluates neuropsychological tests as potential outcome predictors for road tests or in-clinic driving assessments. However, prediction of driving test outcomes is not the same as prediction of crash risk; patients who failed road tests or in-clinic driving assessments would either not be allowed to drive or at least advised not to drive, depending on the laws of the particular state or country of residence. Thus, they would not be expected to be at risk for motor vehicle crash (unless they disregard laws or advice). Whether neuropsychological testing can identify stroke patients at increased risk of crash who were able to pass a road test has not been evaluated in the currently available literature.

***Indirect Evidence–Studies of Driving Performance**: Twelve studies (median quality: moderate) with 879 patients who had experienced stroke evaluated various neuropsychological tests as potential outcome predictors for road tests or in-clinic driving assessments. Eleven of 12 studies found that one or more neuropsychological tests were significant predictors of the outcome of road tests or driving evaluations in this patient population. These findings could not be combined in a quantitative analysis because no two studies used the same array of tests or evaluated the same combination of variables when attempting to identify predictors of outcome. However, certain tests were found to be significant outcome predictors in multiple studies. Figure of Rey was identified as a significant outcome predictor in three out of five studies that used it.(145,149,154) The dot cancellation test, part of the SDSA, was found to be a significant outcome predictor in four out of four studies.*(145,148,153,154) *Another SDSA test (the Road Sign Recognition test) was found to be a significant outcome predictor in two out of four studies.(148,153) A third SDSA test (What Else is in the Square test) was a significant outcome predictor in two out of three studies.(153,154) Two out of three studies that used the Motor-Free Visual Perception Test (MVPT) identified it as a significant outcome predictor.(150,151) Given the moderate quality of the studies and the consistency of the findings for neuropsychological tests overall, the strength of evidence supporting the ability of these tests to predict driving test outcomes is moderate.*

Since the majority of studies did not report the percentage of CMV drivers (if any) in their study population, the generalizability of these findings to CMV drivers is unknown.

Key Question 3: Among individuals who have experienced a transient ischemic attack (TIA), what is the risk of experiencing a future stroke?

Introduction

TIA is defined as a brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia lasting less than 24 hours and without evidence of infarction.(155-157) TIAs occur when a blood clot temporarily blocks an artery, and part of the brain does not receive the blood it needs. Most TIAs last less than five minutes and, unlike stroke, there is no injury to the brain. The rapid onset symptoms of TIA—numbness or weakness of the face, arm or leg, especially on one side of the body; confusion, trouble speaking or understanding; trouble seeing in one or both eyes; trouble walking, dizziness, loss of balance or coordination; and severe headache with no known cause—are similar to those of stroke, but last only a short time. North American guidelines suggest that assessment and investigation should be completed within one week of the TIA, and United Kingdom guidelines recently changed its recommended assessment from two to four weeks to one week.(158,159)

Approximately 200,000 to 500,000 Americans are diagnosed with TIA each year.(160) The true incidence of TIA is not known because many individuals with TIA never seek medical attention and some events are mistakenly diagnosed as TIA but have other etiologies.(156,160) It has been reported that the annual incidence of first-ever TIA in a North American population is 44.1 per 100,000 individuals, increasing to 68.2 per 100,000 individuals for all TIA.(156) About 15 percent to 20 percent of stroke patients report a preceding TIA.(156,158-160)

In this section of the evidence report we attempt to identify the risk of experiencing a future stroke in individuals who have suffered a TIA.

Identification of Evidence Base

To meet the aims of this section of the evidence report we searched for trials that compared the risk of experiencing a stroke among individuals who have experienced a TIA and otherwise comparable individuals who did not experience a TIA. In addition, we looked for studies that compared the prevalence of TIA among cohorts of individuals who have or have not experienced a stroke.

The evidence base identification pathway for Key Question 3 is summarized in Figure 11. Our searches[1] identified a total of 375 articles that appeared relevant to this key question. Following application of the retrieval criteria for this question, 126 full-length articles were retrieved and read in full. Of the 126 retrieved articles, 13 were found to meet the inclusion criteria[2] for Key Question 3 (Table 38). Table D-3 of Appendix D lists the 113 articles retrieved, read in full, and then excluded. The table also provides justification for their exclusion.

[1] See Appendix A for search strategies
[2] See Appendix C for inclusion criteria

Figure 11. Development of Evidence Base for Key Question 3

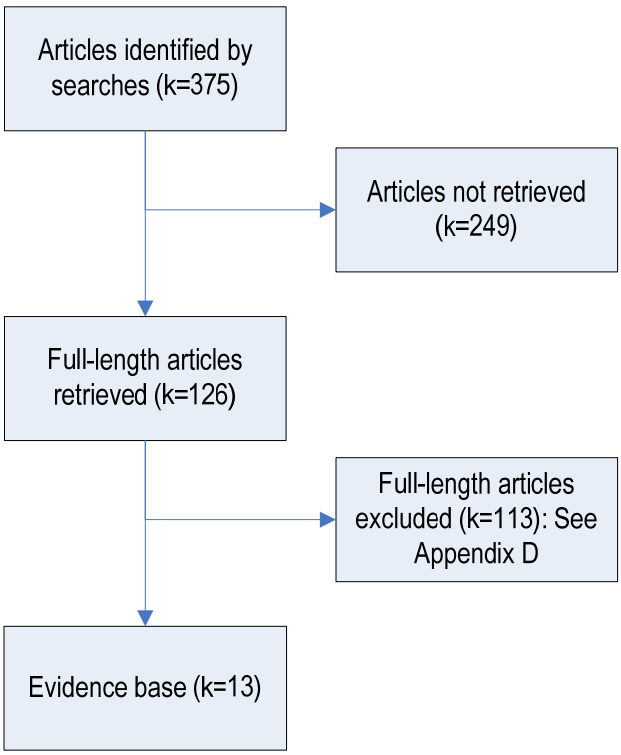


Table 38. Evidence Base for Key Question 3

Reference	Year	Study Location	Country
Harmsen et al.(161)	2006	Göteborg	Sweden
Hajat et al.(162)	2004	London	England
Rodgers et al.(163)	2004	Northumberland	England
de Champvallins et al.(164)	2001	Multiple Sites	France
Kaarisalo et al.(165)	2000	Turku	Finland
Zodpey et al.(166)	2000	Nagpur	India
Whisnant et al.(167)	1996	Minnesota	USA
Howard et al.(168)	1994	North Carolina	USA
Dennis et al.(169)	1990	Oxfordshire	England
Whisnant and Wiebers(170) *	1987	Minnesota	USA
Herman et al.(171)	1983	Tilburg	Netherlands
Ostfeld et al.(172)	1973	Illinois	USA
Whisnant et al.(173)	1973	Minnesota	USA

* Re-analyzes data from Whisnant et al., 1973(173) using population of Rochester, MN, 1960–1964.

Evidence Base

This subsection provides a brief description of the key attributes of the 13 studies that comprise the evidence base for Key Question 3. Here we discuss applicable information onthe quality of the included studies and the generalizability of each study's findings to drivers of CMVs.

Characteristics of Included Studies

The primary characteristics of the 13 included studies that address Key Question 3 are presented in Table 39. Two different study designs (case-control and cohort) characterize the studies included in the evidence base for this key question. One study design (the case-control design) compared the prevalence of TIA among individuals who had experienced a stroke (cases) and a comparable group of individuals who had not experienced a stroke (controls). In studies that used the alternative study design (the cohort design), cohorts were created on the basis of whether individuals had experienced a TIA. The incidence of stroke in these two groups was then compared. Within the cohort design, a group of individuals with TIA were selected and followed up during a specified time interval to determine stroke occurrence.

A design problem common to many risk-assessment studies is the failure to control adequately for exposure. In this instance, the exposure variables of critical importance consisted of whether individuals with recurrent TIAs were included and the time frame over which data were collected. If cases and controls were not well matched for exposure to risk, then any observed differences in risk may simply have been the consequence of differences in exposure. A majority of the included studies enrolled individuals with recurrent TIAs; however, a majority of the included studies attempted to control for time by following cases and controls for the same time periods.

All eight included case-control studies assessed the prevalence of TIA in individuals who did or did not experience a stroke; however, there was a slight difference across studies in the type of stroke evaluated. The majority (5 studies) reported on any type of stroke. In contrast, Hajat et al.(162) and Whisnant et al.(167) analyzed the prevalence of TIA only for individuals who had experienced an ischemic stroke. Zodpey et al.(166) focused their attention on individuals who had experienced a hemorrhagic stroke. All five included cohort studies assessed the incidence of stroke in individuals who experienced a TIA, with three studies(169,170,173) excluding individuals who had recurrent TIAs.

Data from which the incidence of stroke and the prevalence of TIA were determined were obtained primarily from review of medical records, self-report, or questionnaire. Because we cannot determine the accuracy of information from these sources, the degree of confidence that one may have in data extracted from these sources is unclear. Furthermore, these studies may have differed in how they defined TIA or stroke (varying symptoms, medical records) when reported.

Table 39. Key Study Design Characteristics of Studies that Address Key Question 3

Reference	Year	Study Design	Number of Individuals	Community-based vs. Hospital-based Cohort	Recurrent TIA Included	Factors controlled for (if compared to controls)?	Primary Outcome	Definition of TIA	Time from TIA to study entry	Method of outcome ascertainment	Follow-up period
Harmsen et al.(161)	2006	Case-Control Study*	1,019 individuals who had a first-ever stroke during a 28 year period and 6,438 individuals who were stroke free after 28 years	Community	Yes	None	Risk of stroke given previous TIA during baseline using hazard ratio	A history of TIA was considered present if previous focal neurological symptoms lasting <24 hours were reported.	NA	Passive (review of medical records)	28 years
Hajat et al.(162)	2004	Case-Control Study*	664 individuals with a first-ever ischemic stroke and 716 individuals without an ischemic stroke	Community	Yes	None	Risk of stroke given previous TIA using odds ratio	NR	NA	Passive (register, questionnaire, self-report)	All individuals with ischemic stroke between January 1, 1995 and December 31, 1999
Rodgers et al.(163)	2004	Case-Control Study*	329 individuals who experienced a first-ever stroke and 4,022 individuals who were stroke free	Community	Yes	None	Risk of stroke given previous TIA during baseline using hazard ratio	TIA was defined as acute loss of focal cerebral or ocular function with symptoms lasting <24 hours due to embolic or thrombotic disease.	NA	Passive (review of medical records)	5 years
de Champvallins et al.(164)	2001	Case-Control Study*	197 individuals who experienced a stroke and 8,649 individuals who were stroke free	Hospital	Yes	None	Risk of stroke given previous TIA during baseline using odds ratio	NR	NA	Passive (review of medical records)	3 years
Kaarisalo et al.(165)	2000	Case-Control Study*	71 individuals who experienced a stroke and 961 individuals who were stroke free	Community	Yes	None	Risk of stroke given previous history of TIA using hazard ratios	NR	NA	Passive (review of medical records or self-report)	6 years

Reference	Year	Study Design	Number of Individuals	Community-based vs. Hospital-based Cohort	Recurrent TIA Included	Factors controlled for (if compared to controls)?	Primary Outcome	Definition of TIA	Time from TIA to study entry	Method of outcome ascertainment	Follow-up period
Zodpey et al.(166)	2000	Case-Control Study*	166 individuals who experienced a hemorrhagic stroke and 166 individuals who were stroke free	Hospital	Yes	Age and Gender	Risk of stroke given previous history of TIA using odds ratios	NR	NA	Passive	NR
Whisnant et al.(167)	1996	Case-Control Study*	931 individuals who experienced a ischemic stroke and 931 individuals who were stroke free	Community	Yes	Age, gender, date of stroke, duration of medical record at the time of the stroke diagnosis	Risk of stroke given previous history of TIA using odds ratios	NR	NA	Passive (review of medical records)	15 years
Howard et al.(168)	1994	Cohort Study†	280 individuals with TIA and 399 individuals with a comparable cardiovascular risk factor burden who did not have TIA	Hospital	NR	Cardiovascular risk factors	Hazard ratio for stroke risk	NR	NR	Passive (review of medical records)	Median >2 years (range, 6 months to 4 years)
Dennis et al.(169)	1990	Cohort Study†	184 individuals with TIA and 184 individuals who did not have TIA	Community	No	Age and gender	Risk of stroke reported as a risk ratio	A TIA was defined as an acute loss of focal cerebral or ocular function with symptoms lasting <24 hours and which after adequate investigation was presumed to be due to embolic or thrombotic vascular disease.	Median 6 days	Active (medical examination)	Mean 3.7 years (range: 2 days to 7 years)
Whisnant and Wiebers(170)[a]	1987	Cohort Study†	184 individuals with TIA and the population of Rochester, Minnesota from 1960 to 1964	See Whisnant et al., 1973(173) below.							

Reference	Year	Study Design	Number of Individuals	Community-based vs. Hospital-based Cohort	Recurrent TIA Included	Factors controlled for (if compared to controls)?	Primary Outcome	Definition of TIA	Time from TIA to study entry	Method of outcome ascertainment	Follow-up period
Herman et al.(171)	1983	Case-Control Study*	132 individuals who experienced a stroke and 239 individuals who were stroke free	Hospital	Yes	Age and gender	Risk of stroke given previous history of TIA using relative risks	TIA was defined as acute focal deficits of the brain or of the retina, of vascular origin, which last no longer than 24 hours.	NA	Passive (questionnaire)	All individuals with stroke between October 1,1978 and July 31,1981
Ostfeld et al.(172)	1973	Cohort Study†	176 individuals with TIA and 2,596 individuals without TIA	Community	Yes	Age	Incidence of stroke	A TIA was diagnosed if there was a history of focal neurological dysfunction which met the criteria for completed stroke except that the deficit lasted less than 24 hours and there were no detectable residua.	NR	Active (medical examination)	3 years
Whisnant et al.(173)	1973	Cohort Study†	198 individuals with TIA and the population of Rochester, Minnesota from 1955 to 1969	Community	No	Age and gender	Risk of stroke	A TIA was defined as an episode of focal neurologic symptoms with abrupt onset and rapid resolution, lasting less than 24 hours, and due to altered circulation to a limited region of the brain.	NR	Passive (review of medical records)	10 years

* A case-control study in which cases are defined according to whether individuals have experienced a stroke and controls consist of a cohort of individuals who have not experienced a stroke.

† A cohort study in which cases are defined according to the presence of a TIA and controls consist of a cohort of individuals who have not experienced a TIA.

[a] Re-analyzes data from Whisnant et al., 1973(173) using population of Rochester, Minnesota from 1960 – 1964.

NA = Not Applicable
TIA = Transient Ischemic Attack

Quality of Evidence Base

The findings of our assessment of the quality of the studies that comprise the evidence base for Key Question 3 are summarized in Table 40. Complete details of our quality assessment can be found in the Quality Score Tables in Appendix G.

All included studies were rated as either of low or moderate quality. The quality of case-control and cohort studies is limited because of non-random allocation of individuals to different groups. Although observational studies often statistically adjust for known confounding factors, only random allocation can control for unknown confounding factors; however, random allocation is not possible in these study designs. Therefore, the quality rating of these studies can never be high.

Table 40. Quality of the Studies that Assess Key Question 3

Reference	Year	Quality Scale Used	Quality
Harmsen et al.(161)	2006	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Hajat et al.(162)	2004	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Rodgers et al.(163)	2004	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
de Champvallins et al.(164)	2001	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Kaarisalo et al.(165)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Zodpey et al.(166)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Whisnant et al.(167)	1996	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Moderate
Howard et al.(168)	1994	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Dennis et al.(169)	1990	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Whisnant and Wiebers(170) *	1987	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Herman et al.(171)	1983	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Ostfeld et al.(172)	1973	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Whisnant et al.(173)	1973	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate

* Re-analyzes data from Whisnant et al., 1973(173) using population of Rochester, Minnesota from 1960 – 1964.

Generalizability of Evidence to Target Population

Our assessment of the generalizability of the findings of the studies that form the evidence base for Key Question 3 is based on the characteristics of the individuals enrolled in each of the included studies. These characteristics are presented in Table 41. Subjects were recruited from two settings, community-based and hospital-based settings. None of the included studies specifically sought to recruit a population of CMV drivers. While it is possible that some CMV drivers were included among the enrollees in these studies, none report on the number they included. Consequently, the degree to which the findings of the included studies can be generalized to CMV drivers is uncertain. In an attempt to assess the comparability of subjects in the included studies to CMV drivers, we assessed the age, sex, and ethnicity of the included subjects. The mean age of enrolled subjects (where reported) ranged widely, from 61 to 79,

however subjects could have been as young as 40 years and as old as 85 years. The proportion of males enrolled in the studies varied greatly, ranging (where reported) from 30 percent to 100 percent. Compared with a CMV driver population, these studies have (on average) an older population and a greater proportion of women. Not all studies reported the race of enrolled subjects, but among those that did, the proportion of Caucasian subjects ranged from 32 percent to 78 percent, with African Americans comprising the rest of the population.

Table 41. Individuals with a TIA or Stroke Enrolled in Studies that Address Key Question 3

Reference	Year	Number of Individuals	Age Distribution	% Male	% CMV Drivers	Ethnicity	Generalizability to Target Population
Harmsen et al.(161)	2006	*Cases*: 1,019 *Controls*: 6,438	Range, 47-55	100	NR	NR	Unclear
Hajat et al.(162)	2004	*Cases*: 664 *Controls*: 716	Range, 45-74	*Cases*: 51.4* *Controls*: 30.2*	NR	*Cases*: Caucasian: 78 Black Caribbean: 16 Black African: 6 *Controls*: Caucasian: 42 Black Caribbean: 43 Black African: 15	Unclear
Rodgers et al.(163)	2004	*Cases*: 329 *Controls*: 4,022	*Cases*: 78.6 ±6.3 *Controls*: 75.9 ±6.8	*Cases*: 46.8 *Controls*: 45.8	NR	NR	Unclear
de Champvallins et al.(164)	2001	*Cases*: 197 *Controls*: 8,649	*Cases*: 76.7 ±6.9 *Controls*: NR	*Cases*: 39.1* *Controls*: 38.2*	NR	NR	Unclear
Kaarisalo et al.(165)	2000	*Cases*: 71 *Controls*: 961	Age 70 years at baseline	*Cases*: 53.5 *Controls*: 46.5	NR	NR	Unclear
Zodpey et al.(166)	2000	*Cases*: 166 *Controls*: 166	*Cases (%):* ≤50 yrs 4.82 51-60 yrs 19.28 61-70 yrs 52.41 >70 yrs 23.49 *Controls (%):* ≤50 yrs 4.82 51-60 yrs 19.28 61-70 yrs 52.41 >70 yrs 23.49	*Cases*: 59.04 *Controls*: 59.04	NR	NR	Unclear
Whisnant et al.(167)	1996	*Cases*: 931 *Controls*: 931	NR	NR	NR	NR	Unclear
Howard et al.(168)	1994	*Cases*: 280 *Controls*: 399	*Cases*: 64 *Controls*: 61	*Cases*: 50 *Controls*: 65	NR	African-American: *Cases*: 6 *Controls*: 5	Unclear
Dennis et al.(169)	1990	*Cases*: 184 *Controls*: 184	*Cases*: 69.4 *Controls*: NR	*Cases*: 56 *Controls*: NR	NR	NR	Unclear

Reference	Year	Number of Individuals	Age Distribution	% Male	% CMV Drivers	Ethnicity	Generalizability to Target Population
Whisnant and Wiebers(170) †	1987	*Cases*: 184 *Controls*: 39,012 – 46,698 (population of Rochester, MN from 1960 – 1965)	See Whisnant et al., 1973(173) below.				
Herman et al.(171)	1983	*Cases*: 132 *Controls*: 239	*Cases (%):* 40-49 yrs 9.1* 50-59 yrs 30.3* 60-69 yrs 34.1* 70-74 yrs 26.5* Controls (%): 40-49 yrs 9.2* 50-59 yrs 32.2* 60-69 yrs 32.2* 70-74 yrs 26.4*	*Cases*: 63 *Controls*: 64	NR	NR	Unclear
Ostfeld et al.(172)	1973	*Cases*: 176 *Controls*: 2,596	Range: 65-74	*Cases*: 40.9 *Controls*: 48.2	NR	*Cases*: Caucasian: 31.8 African-American: 68.2 *Controls*: Caucasian: 44.6 African-American: 55.4	Unclear
Whisnant et al.(173)	1973	*Cases*: 198 *Controls*: 32,600-52,629 (population of Rochester, MN from 1955-1970)	*Cases*: 70 *Controls*: NR	*Cases*: 44 *Controls*: NR	NR	NR	Unclear

* Calculated by ECRI Institute from reported data

† Re-analyzes data from Whisnant et al., 1973(173) using population of Rochester, MN 1960–1964.

Unless otherwise stated, data are expressed as mean ±SD

CMV = Commercial motor vehicle.
CWS = Capsular Warning Syndrome.
NR = Not reported.
SD = Standard deviation.
TIA = Transient Ischemic Attack.

Findings

As stated previously, the evidence base for Key Question 3 is composed of two distinct types of studies. Five studies compared stroke risk among individuals with a TIA to a comparable group of individuals who did not experience a TIA. Eight studies compared the prevalence of TIA among individuals who had experienced a stroke (cases) to a comparable group of individuals who did not experience a stroke (controls). Although both types of studies may be considered to address the same question from a qualitative perspective ("Does having a TIA represent an increased risk for a stroke?"), they differ significantly from a quantitative perspective. Outcome

data from the former set of studies were presented as a Risk Ratio[3]. Outcome data from the latter group of studies were presented as an Odds Ratio[4].

Our searches did identify one systematic review/meta-analysis by Wu et al.(155), that attempted to estimate the risk of stroke at 2, 30, and 90 days after TIA. Their searches identified 51 candidate studies reporting early risk of stroke after TIA. Two reviewers independently extracted information from 11 selected studies. The 11 included studies recruited a total of 7,238 individuals. The smallest included trial studied 62 individuals and the largest 2,285. Based on a random effects model, the pooled early risk of stroke was 3.5 percent, 8.0 percent, and 9.2 percent at 2, 30, and 90 days after TIA, respectively. As a result, the authors concluded that TIA is associated with high early risk of stroke. However, it should be noted that only one(173) of the 11 studies included in the meta-analysis of Wu et al. used a control group for comparison. The use of a control group was a specific criteria needed in order for a study to be included in our analysis; as a result, our analysis included only one(173) of the 11 studies used in Wu et al.

Studies of Effect of TIA on Stroke Risk

Thirteen included studies provided data on the influence of TIA on the risk of stroke. Collectively, these studies provide strong evidence of a significantly increased risk of TIA. Because this risk may be affected by the duration of time elapsed since TIA, and because stroke risk was assessed using two different analytic approaches in various studies, we performed more specific analyses based on time since TIA and the analytic approach used in each study.

The first approach to determining the risk of stroke associated with a TIA is to compare the prevalence of a TIA among a group of individuals who had experienced a stroke with that observed among a group of individuals who had not experienced a stroke. The difference in stroke risk measured by this type of study is usually the Odds Ratio (the odds of having a TIA having experienced a stroke divided by the odds of having a TIA having not experienced a stroke). For ease of communication, we henceforth refer to these studies as "OR studies."

The second approach is to compare the incidence of stroke among individuals who have experienced a TIA with the incidence of stroke among comparable individuals who did not experience a TIA. The measure of the difference in stroke risk reported by this type of study is usually the Risk Ratio (the ratio of stroke incidence observed among individuals with a TIA and comparable individuals who did not have a TIA). Henceforth, we refer to these studies as "RR studies."

[3] The incidence of stroke among individuals with a TIA divided by the incidence of stroke among comparable individuals who did not have a TIA.

[4] The odds of an individual who experienced a stroke having had a TIA, divided by the odds of an individual who did not experience a stroke having had a TIA.

TIA and Stroke Risk: Findings of the OR Studies

Eight of the 13 studies presented data on the odds of an individual who experienced a stroke of having a TIA relative to the odds of a comparable individual who did not experience a stroke of having a TIA.(161-167,171) The findings of these studies are summarized in Table 42 below.

Table 42. Findings of Case-Control Studies

Reference	Year	Number of Individuals	Follow-up period	Stroke Risk Data					Evidence of Increased Stroke Risk
				% with TIA (Cases - Stroke)	% with TIA (Controls - No stroke)	Effect Size (95% CI)	Factors adjusted for:	*p*-value	
Harmsen et al.(161)	2006	*Cases*: 1,019 *Controls*: 6,438	28 years	2 (of total study population)		HR = 1.78 (1.21 – 2.63)	Age	NR	Yes
						HR = 1.74 (1.14 – 2.64)	All other risk factors†	NR	Yes
			0 – 15 years			HR = 2.39 (1.31 – 4.37)	Age	NR	Yes
						HR = 1.79 (0.88 – 3.67)	All other risk factors†	NR	No
			16 – 21 years			HR = 2.45 (1.30 – 4.61)	Age	NR	Yes
						HR = 3.01 (1.58 – 5.74)	All other risk factors†	NR	Yes
			22 – 28 years			HR = 0.85 (0.35 – 2.05)	Age	NR	No
						HR = 0.91 (0.37 – 2.22)	All other risk factors†	NR	No
Hajat et al.(162)	2004	*Cases*: 664 *Controls*: 716	NR	16.1*	2.1*	OR = 20.5 (10.02 – 42.04)	Age, gender, and socio-economic status	<0.001	Yes
Rodgers et al.(163)	2004	*Cases*: 329 *Controls*: 4,022	5 years	12.5	5.5	OR = 2.46* (1.73 – 3.51)	None	<0.001*	Yes
						HR = 2.18 (1.57 – 3.04)	Age and gender	NR	Yes
						HR = 1.87 (1.27 – 2.76)	All other risk factors‡	NR	Yes
de Champvallins et al.(164)	2001	*Cases*: 197 *Controls*: 8,649	3 years	19.2	9.4*	OR = 2.29* (1.60 – 3.29)	None	<0.001*	Yes
Kaarisalo et al.(165)	2000	*Cases*: 71 *Controls*: 961	6 years	22.5	5.0	OR = 5.52* (2.94 – 10.34)	None	<0.001*	Yes
						HR = 4.14 (2.30 – 7.45)	None	0.0001	Yes

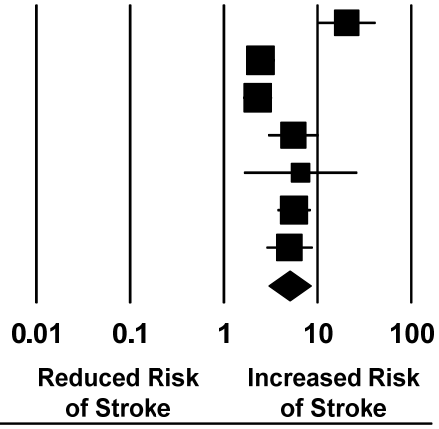
Reference	Year	Number of Individuals	Follow-up period	Stroke Risk Data					Evidence of Increased Stroke Risk
				% with TIA (Cases - Stroke)	% with TIA (Controls - No stroke)	Effect Size (95% CI)	Factors adjusted for:	*p*-value	
Zodpey et al.(166)	2000	*Cases*: 166 *Controls*: 166	NR	NR	NR	OR = 6.66 (1.98 – 22.41) OR = 6.58 (1.62 – 26.67)	Univariate Analysis Multivariate Analysis	NR 0.0083	Yes Yes
Whisnant et al.(167)	1996	*Cases*: 931 *Controls*: 931	15 years	17.2*	3.7*	OR = 5.6 (3.70 – 8.52)	Age, date of stroke, and interaction between age and time period	0.0001	Yes
Herman et al.(171)	1983	*Cases*: 132 *Controls*: 239	NR	33	9	OR = 5.02* (2.82 – 8.93) RR = 5.22 (2.98 – 9.13) RR = 7.32 (3.01 – 17.83)	None Age and gender Age, gender, and all other risk factors††	<0.001* NR NR	Yes Yes Yes

CI = Confidence Interval
NR = Not Reported
NS = Not Significant
RR = Relative Risk.
TIA = Transient Ischemic Attack
* Calculated by ECRI Institute from reported data
† see Table 2 in Harmsen et al., 2006(161) for list of factors
‡ see Table 2 in Rodgers et al., 2004(163) for list of factors
†† see Table 3 in Herman et al., 1983(171) for list of factors

Seven of the eight included studies (Quality Rating: Low) provided enough data to determine the Odds Ratio and 95 percent confidence intervals for the incidence of TIA among individuals who have experienced a stroke and comparable individuals who have not experienced a stroke.(162-167,171,174-180) We could not perform separate analyses based on length of follow-up because this varied considerably among these studies. Thus, we chose to pool the data from these seven studies in one meta-analysis. Heterogeneity testing revealed substantial differences among the findings of the seven studies (I^2 =85.3 percent), which precluded determining a quantitative summary estimate of effect. Because the evidence base consisted of less than 10 studies, we did not attempt to explore this heterogeneity using meta-regression techniques[5]. Rather, we pooled these data using a random-effects meta-analysis to allow a qualitative conclusion about the direction of effect (Figure 12).

Figure 12. TIA and Stroke Risk (OR)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Hajat 2004	20.500	10.008	41.991	8.256	0.000
Rodgers 2004	2.460	1.726	3.506	4.981	0.000
Champvallins 2001	2.290	1.595	3.289	4.489	0.000
Kaarisalo 2000	5.516	2.944	10.337	5.329	0.000
Zodpey 2000	6.580	1.622	26.698	2.637	0.008
Whisnant 1996	5.600	3.690	8.498	8.096	0.000
Herman 1983	5.016	2.816	8.932	5.477	0.000
Summary	**NC**	**2.965**	**8.360**	**6.069**	**0.000**



NC – Not calculated

The findings of this meta-analysis provide support for the contention that there is an increased incidence of TIA among individuals who have experienced a stroke when compared with individuals who have not experienced a stroke (OR 95 percent CI: 2.97-8.36, $p < 0.001$). A series of sensitivity analyses (Appendix H) demonstrated our finding to be robust. While the quality of the studies was low, the data were qualitatively consistent, and the lower 95 percent confidence limit of the magnitude of effect is very large. Consequently, one can be reasonably confident that future research findings are unlikely to overturn our findings.

One study, by Harmsen et al.(161), was not included in the above analysis because the authors reported their findings in the form of hazard ratios, and did not report enough data from which an

[5] ECRI Institute requires at least 10 studies for meta-regression or subgroup analysis to be attempted.

odds ratio and 95 percent confidence intervals could be determined. However, the findings of Harmsen et al. were similar to those studies included in the analysis above, and provide further support for our findings. Harmsen et al. reported that the age-adjusted hazard ratio for stroke in individuals with previous TIA was 1.78 (95 percent CI: 1.21-2.63).

TIA and Stroke Risk: Findings of the RR Studies

Five included studies reported on the incidence of strokes occurring among populations of individuals with a TIA and the incidence of strokes occurring among individuals who did not have a TIA.(168-170,172,173) Two of these studies(170,173) used the same individuals who experienced a TIA. One study, Whisnant and Wiebers(170), compared this TIA group to the population of Rochester, MN for the years 1960 through 1964. The other study, Whisnant et al.(173), compared the TIA group to the population of Rochester, MN for the years 1955 through 1969. Because Whisnant and Wiebers reported their results in such a way that allowed ECRI Institute to determine the risk of stroke following a TIA, we included this study in the analyses below. The findings of the four included studies (Quality Rating: Moderate) are presented in Table 43 below.

Table 43. Stroke Risk in Individuals with a TIA compared to Individuals without a TIA

Reference	Year	Units	Incidence of Stroke Data									Evidence of Increased Stroke Risk
			TIA group			Control group			Hazard or Risk Ratio (95% CI)	Adjusted for…	*P* =	
Howard et al.(168)	1994		Stroke Rate, %			Stroke Rate, %			Hazard Ratio			
			1 yr	2 yrs	3 yrs	1 yr	2 yrs	3 yrs				
			5.4	6.3	7.8	1.5	2.1	2.7	3.0	Unadjusted	0.0061	Yes
			4.2	6.2	7.9	1.2	1.7	2.2	3.6	Age, ethnicity, gender	0.0023	Yes
			2.5	3.9	5.6	0.6	0.9	1.3	4.5	Age, ethnicity, gender, major cardiovascular risk factors	0.0030	Yes
Dennis et al.(169)	1990	*By gender:*	Observed number of strokes			Expected number of strokes			Risk Ratio			
		Males	22			3.6			6.2 (3.9 – 9.4)		<0.0001	Yes
		Females	23			2.9			8.0 (5.0 – 11.9)		<0.0001	Yes
		By age:							Risk Ratio			
		<75 years	25			1.9			13.2 (8.5 – 19.4)		<0.0001	Yes
		≥75 years	20			4.4			4.5 (2.8 – 7.0)		<0.0001	Yes
		By follow-up:							Risk Ratio			
		≤1 month	8			0.1			80.0 (34.0 – 158.0)		<0.0001	Yes
		≤6 months	16			0.6			27.0 (15.2 – 43.2)		<0.0001	Yes
		≤12 months	20			1.5			13.4 (8.2 – 20.7)		<0.0001	Yes
		1-2 years	7			1.5			4.7 (1.9 – 9.6)		0.001	Yes
		2-3 years	6			1.3			4.7 (1.7 – 10.0)		0.002	Yes
		3-4 years	6			0.9			6.4 (2.4 – 14.6)		<0.0001	Yes
		4-5 years	4			0.7			5.8 (1.6 – 14.6)		0.006	Yes
		5-6 years	2			0.4			5.0 (0.6 – 22.0)		0.06	No
		6-7 years	0			0.2			0.0 (0.0 – 18.5)		NS	No
		Total:	45			6.5			7.0 (5.1 – 9.3)		<0.0001	Yes

Reference	Year	Units	Incidence of Stroke Data					Evidence of Increased Stroke Risk
			TIA group	Control group	Hazard or Risk Ratio (95% CI)	Adjusted for…	*P* =	
Whisnant and Wiebers(170)	1987		**Probability of stroke, given survival**	**Expected probability of stroke**	**Observed to Expected Ratio**			
		1 month	0.08	0.00067	119.4 (65.4-218.1)*		NR	Yes
		6 months	0.10	0.004	25 (15.5-40.3)*		NR	Yes
		1 year	0.13	0.008	16.3 (10.7-24.6)*		NR	Yes
		2 years	0.19	0.016	11.9 (8.5-16.6)*		NR	Yes
		3 years	0.25	0.024	10.4 (7.8-14.0)*		NR	Yes
		4 years	0.26	0.032	8.1 (6.0-11.0)*		NR	Yes
		5 years	0.29	0.040	7.3 (5.4-9.7)*		NR	Yes
		6 years	0.31	0.048	6.5 (4.9-8.4)*		NR	Yes
		7 years	0.36	0.056	6.4 (4.9-8.5)*		NR	Yes
		8 years	0.40	0.064	6.3 (4.7-8.4)*		NR	Yes
Ostfeld et al.(172)	1973	**Risk Ratio for stroke after 3 years**	26	157	2.443 (1.661 – 3.593)*	Age adjusted by 5 year intervals	<0.0001	Yes

* Calculated by ECRI Institute; Effect-Size estimates >1.0 indicate that individuals who have experienced a TIA are at increased risk for stroke than comparison group

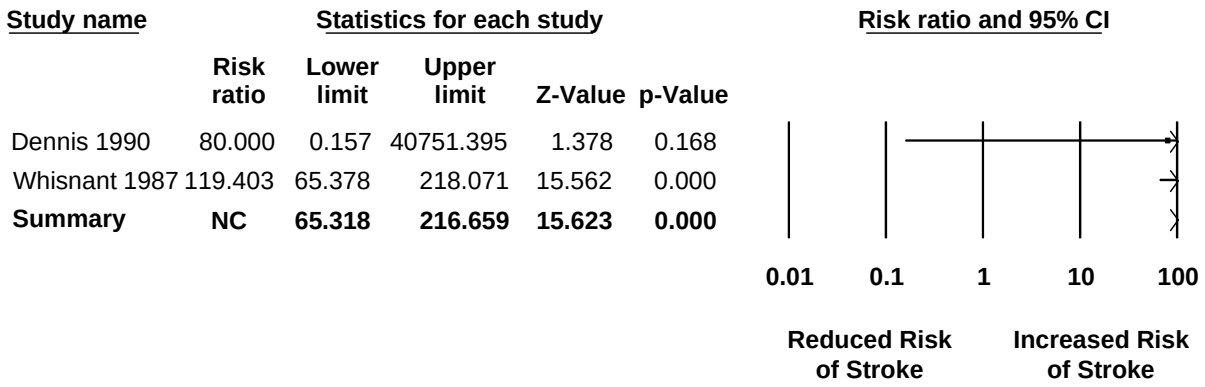
CI = Confidence Intervals
NC = Not Calculated.
NS = Not Significant

Follow-up times reported in the four included studies ranged from one month to eight years. Only those times reported in two or more studies were analyzed and reported separately below.

One Month Follow-up

Two included studies (Quality Rating: Moderate) provided enough data to determine the stroke RR and 95 percent confidence intervals between individuals who have TIA and comparable individuals without TIA after one month. The forest plot (Figure 13) revealed both studies had the same direction of effect, although only one had a statistically significant finding (we used a more conservative approach for calculating a 95 percent CI than the approach used by the study authors). However, a random-effects meta-analysis confirmed that one month after a TIA there is a statistically significant increase in stroke risk. Although a summary effect estimate could not be determined with precision, the lower 95 percent confidence limit showed a very large effect (RR 95 percent CI 65.3 to 216.7). This is at least a 65-fold increase in stroke risk.

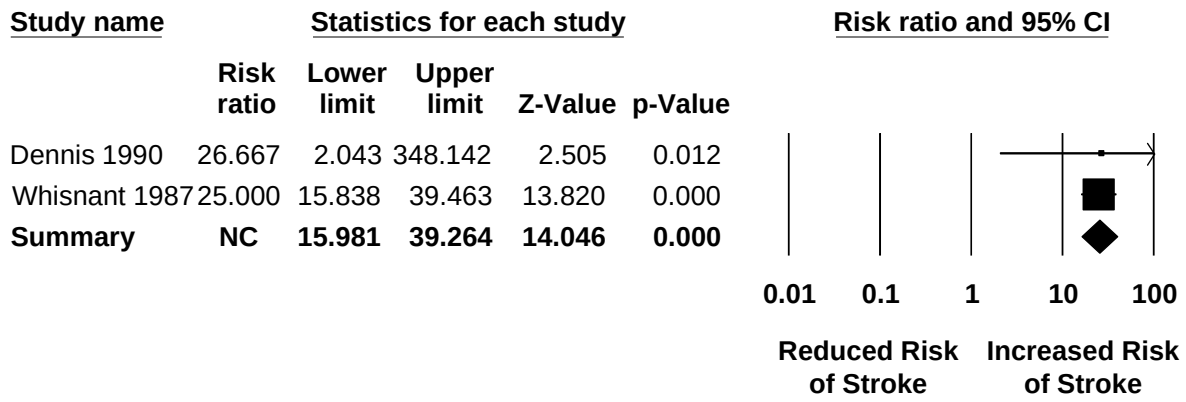
Figure 13. One Month Stroke Risk Among Individuals with TIA Compared to Controls (Random-effects Meta-analysis)



Six-Month Follow-up

The same two studies with one-month data also provided six-month follow-up data. The forest plot (Figure 14) suggests that the data from the two included studies are consistent, and the meta-analysis confirmed that the summary effect is at minimum a 16-fold increase in stroke risk (RR 95 percent CI 16.0 to 39.3).

Figure 14. Six-Month Stroke Risk Among Individuals with TIA Compared with Controls (Random-effects Meta-analysis)

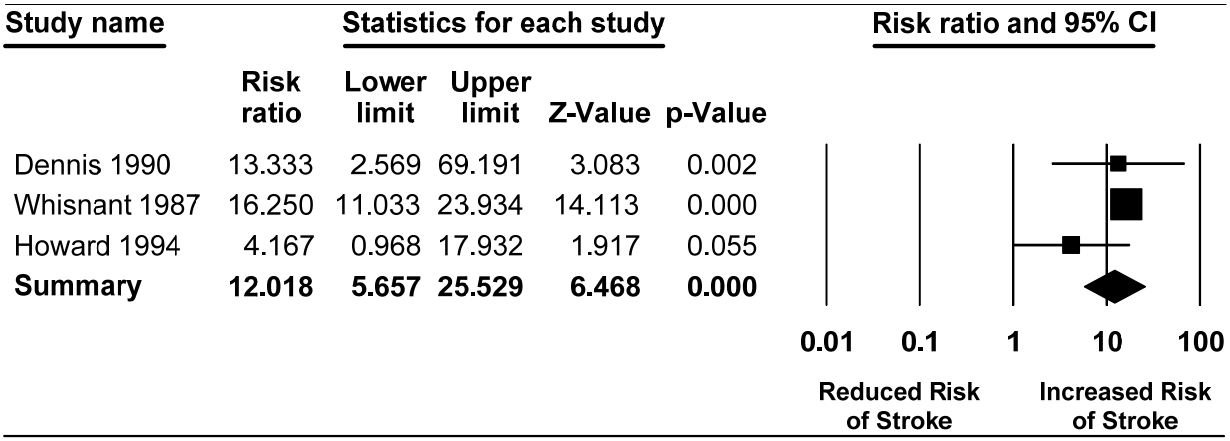


NC – Not calculated.

One Year Follow-up

Three included studies (Quality Rating: Moderate) provided enough data to determine the stroke RR and 95 percent confidence intervals between individuals who have TIA and comparable individuals without TIA after one year.(168-170) Heterogeneity testing did not reveal substantial differences among study results (I^2 = 36.2 percent).(174-180) We pooled these data using a random-effects meta-analysis (Figure 15). The findings of this meta-analysis provide support for the contention that one year following a TIA, individuals are at a significantly increased risk for experiencing a stroke when compared with comparable individuals without TIA (Stroke RR = 12.02, 95 percent CI: 5.66-25.53, $p < 0.001$).A series of sensitivity analyses (Appendix H) demonstrated our finding of increased stroke risk at one year following TIA to be robust.

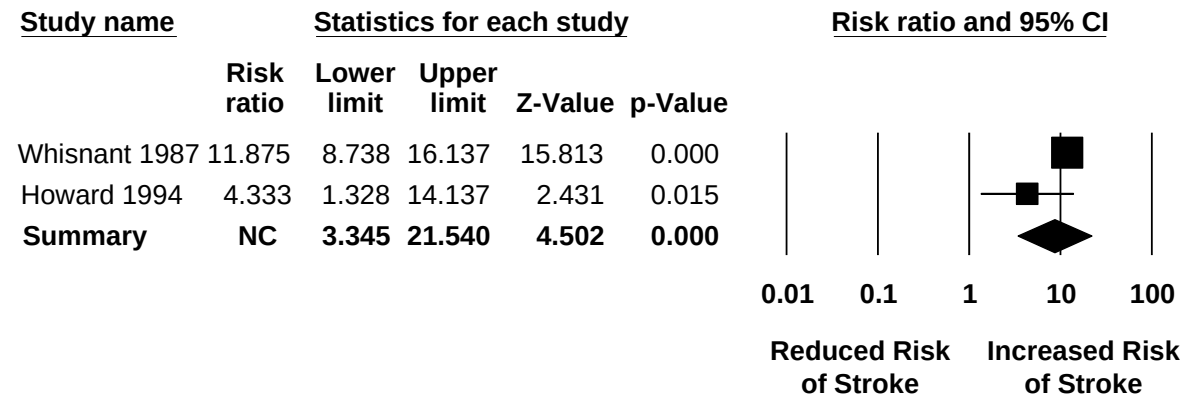
Figure 15. One-Year Stroke Risk Among Individuals with TIA Compared with Controls (Random-effects Meta-analysis)



Two Year Follow-up

Two included studies (Quality Rating: Moderate) provided enough data to determine the stroke RR at two years of follow-up. The forest plot (Figure 16) suggests that the data from these studies are consistent in showing an elevated risk following TIA out to two years. Although we did not attempt to determine a precise quantitative summary estimate with only two studies, a random-effects meta-analysis nevertheless confirmed that the increase in risk is, at minimum, three times higher compared with the control group (RR 95 percent CI 3.3-21.5).

Figure 16. Two Year Stroke Risk Among Individuals with TIA Compared with Controls (Random-effects Meta-analysis)

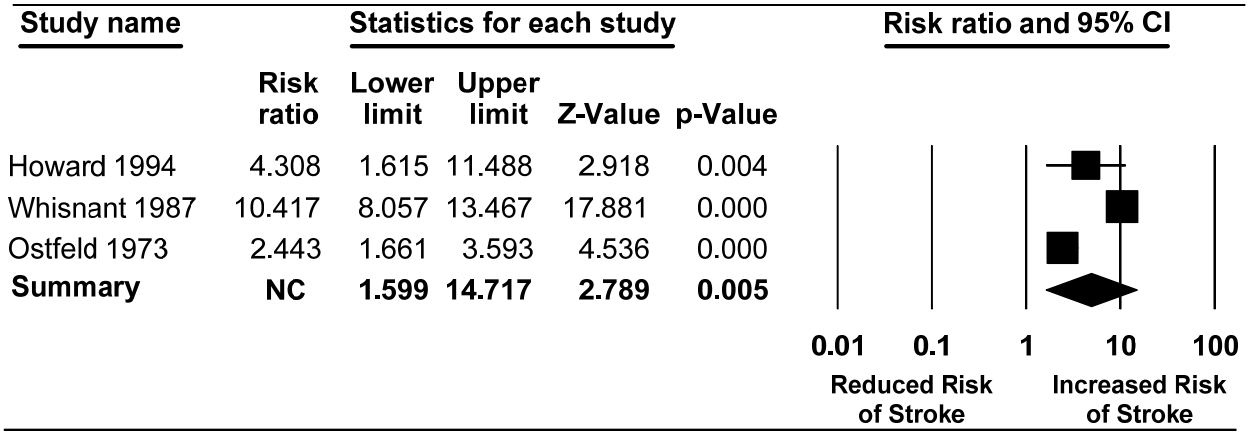


NC – Not calculated.

Three Year Follow-up

Three included studies (Quality Rating: Moderate) provided enough data to determine the stroke RR after three years.(168,170,172) Heterogeneity testing revealed substantial differences among study results (I^2 = 94.8 percent), which precluded a quantitative summary estimate of effect.(174-180) Instead, we pooled these data using a random-effects meta-analysis to reach a qualitative conclusion about the direction of effect (Figure 17). The findings of this meta-analysis support the contention that three years following a TIA, individuals are at a significantly increased risk for experiencing a stroke when compared with comparable individuals without TIA (Stroke RR 95 percent CI: 1.60-14.72, p = 0.005). A series of sensitivity analyses (Appendix H) demonstrated our finding of increased stroke risk at three years following a TIA to be robust.

Figure 17. Three Year Stroke Risk Among Individuals with TIA Compared with Controls (Random-effects Meta-analysis)



NC – Not calculated.

Follow-up beyond Three Years

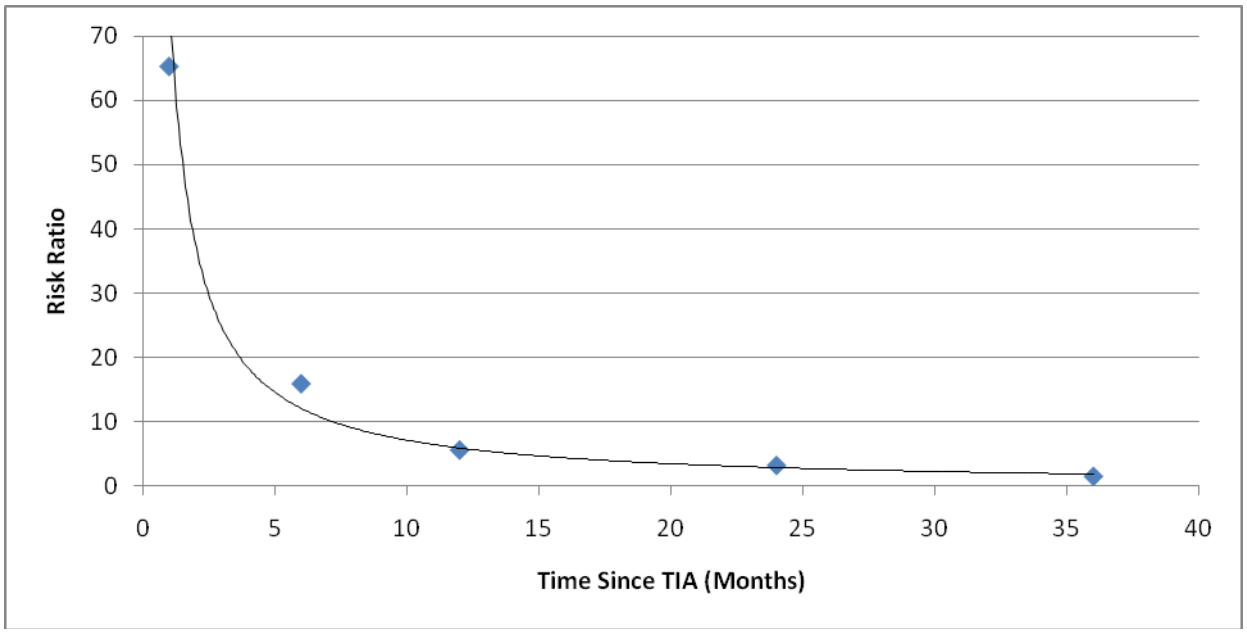
Two studies reported data on relative risk of stroke at four, five, six, and seven years following TIA.(169,170,174-180) We did not combine the data from the later time points of these studies because that would have required too many assumptions about the data in one of the studies. However, both studies show a significantly elevated RR for stroke out to at least five years post-TIA, which is minimally acceptable evidence to support a conclusion.

The RR at six or seven years is less clear because one of the studies (Dennis et al. 1990) did not have enough patients with follow-up out to these time points. The remaining study (Whisnant and Wiebers, 1987) reported significantly elevated RRs at six, seven, and eight years post-TIA. Although these findings are statistically significant, and suggest an elevated stroke risk up to eight years post-TIA, they should be replicated in another study with sufficient patient follow-up before conclusions can be drawn.

Summary of RR studies

The relationship between RR for stroke over time since TIA is shown in Figure 18. The RR used on the curve represents the lower 95 percent confidence limit of the effect estimate for the time points of one month, six months, 12 months, 24 months, and 36 months. Therefore, this is a conservative estimate of the RR for each time point. At one month following TIA, patients have at least a 65-fold increase in the risk of stroke compared with individuals without prior TIA. The cumulative risk for stroke given prior TIA decreases to a minimum RR of 16 times the control risk at six months, six times the control risk at 12 months, three times the control risk at 24 months, and 1.6 times the control risk at 36 months. The data suggest that the risk drops rapidly after the first month, although it remains fairly high during the first year, so this early period following a TIA is of the greatest concern regarding the potential for sudden incapacitating events that could lead to a motor vehicle accident.

Figure 18. Risk Ratio for Stroke Over Time Since TIA



Given the above findings, an important question is whether this excessive early risk of stroke following TIA can be reduced. A recent study in the UK has attempted to address this question. The Early use of Existing Preventive Strategies for Stroke (EXPRESS) study identified all patients who presented with TIA or stroke within a larger population study.(181) The trial was divided into two time periods (phase I and phase 2) which differed in the protocol for clinic assessment and initiation of treatment. Phase 1 patients received usual care at a stroke clinic from 2002 to 2004; the clinic required appointments, and following clinical assessment did not initiate treatment but sent treatment recommendations to the patient's primary care physician. From 2004 to 2007, the study authors evaluated patients at a different clinic where no appointments were necessary and treatment was initiated immediately upon confirmation of diagnosis; this effectively reduced the time to treatment initiation. Patients with TIA who received care at the phase 1 clinic had a 12.4% risk of stroke within the first 90 days, while those who received care at the phase 2 clinic had a 4.4% risk of stroke within the first 90 days (RR = 0.35, a 65% reduction in risk, p = 0.0015). When comparing patients with TIA who received outpatient rather than hospital-based care, the difference in risk was even larger; 9.7% in phase 1 versus 0.6% in phase 2 (RR = 0.06, a 94% reduction in risk, p = 0.0001). However, the relative risk of stroke for these patients compared to patients who had not experienced a cerebral event could not be determined as this study did not include such a control group.

Summary of Findings

A number of conclusions can be drawn from the findings of the analyses described above. These are presented below:

TIA and Stroke Risk: Overall Findings

Individuals are at an increased risk for stroke following a TIA when compared with their counterparts who did not experience a TIA (Strength of Evidence: Strong).

The increased stroke risk is highest immediately following TIA (within one month) and decreases steadily out to five years following TIA (Strength of Evidence: Moderate).

The entire evidence base of 13 studies (representing approximately 30,000 individuals), consistently reported an elevated risk of stroke in individuals who experienced a TIA compared with controls who did not experience a TIA. Separate analyses based on four moderate-quality cohort studies with data at multiple follow-up periods suggests that the increased risk is very high within the first month following TIA (at least 65 times higher than the risk for individuals who have not had a TIA) and drops rapidly during the first year. A small cumulative elevated risk continues to decrease steadily out to five years following TIA.

TIA and Stroke Risk: Findings based on Time Since TIA

At one month and six months following a TIA event, individuals are at an increased risk for stroke when compared with their counterparts who did not experience a TIA (Strength of Evidence: Moderate).

- **A precise estimate of the magnitude of this increased risk cannot be determined at this time.**

Two studies (Quality Rating: Moderate) at each follow-up time presented data directly relevant to these time points. The data were qualitatively consistent and the magnitude of increased risk at each time point examined was large. Although precise summary effect estimates could not be determined, individuals with TIA had at least a 65-fold increase in risk at one month and a 16-fold increase at six months compared with controls without TIA. Therefore, it is unlikely that future studies will overturn our finding.

At one year following a TIA, individuals are at an increased risk for stroke when compared with their counterparts who did not experience a TIA (Strength of Evidence: Strong).

- **The estimated magnitude of increased risk at one year is RR=12.02 (95 percent CI 5.66 to 25.53) (Stability of Evidence: Low).**

Three studies (Quality Rating: Moderate) presented data at one year following TIA. Pooling of these data revealed that the mean stroke risk associated with TIA is RR=12.02 (95 percent CI 5.66 to 25.53) one year after experiencing a TIA, representing a 12-fold increase in risk compared with individuals who have not experienced a TIA. The finding of increased stroke risk was robust, although the stability of the summary effect size was low. The data were qualitatively consistent and the effect size was very large, making it very unlikely that future studies will overturn this finding.

At two and three years following a TIA event, individuals are at an increased risk for stroke when compared with their counterparts who did not experience a TIA (Strength of Evidence: Moderate).

- **A precise estimate of the magnitude of this increased risk cannot be determined at this time.**

Three studies (Quality Rating: Moderate) presented data on stroke risk at three years following TIA. Pooling of these data revealed that the risk of experiencing a stroke three years after a TIA event is at least 1.6 times greater than the control risk level. Two of these studies also evaluated stroke risk at two years, which was found to be elevated by at least three-fold in individuals with TIA compared with controls without TIA.

At four and five years following a TIA event, individuals are at an increased risk for stroke when compared to their counterparts who did not experience a TIA (Strength of Evidence: Minimally Acceptable).

Two studies (Quality Rating: Moderate) at each follow-up time presented data directly relevant to this question. The findings were qualitatively consistent, but the data could not be combined in a pooled analysis. Thus, the evidence is considered minimally acceptable to support the conclusion.

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Appendix A: Search Summaries

Search summary for Key Questions 1 and 2

The search strategies employed combinations of free text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts: accidents, mental disorders, mental disease, driving, and motor vehicle operation. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE, MEDLINE, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

Stroke

Electronic Database Searches

The following databases have been searched for relevant information.

Name	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 through January 10, 2008	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2007, Issue 4	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2007, Issue 4	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2007, Issue 4	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2007, Issue 4	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through January 10, 2008	OVID
MEDLINE	1950 through January 10, 2008	OVID
PreMEDLINE	Searched January 10, 2008	OVID
PsycINFO	Through January 10, 2008	OVID
TRIS	Searched December 18, 2007	
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2007, Issue 4	www.thecochranelibrary.com

Medical Subject Headings (MeSH), EMTREE, PsycINFO and Keywords

Conventions:

OVID

$ = truncation character (wildcard)

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication Type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = Publication Type

[sb] = Subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)

[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)

[tiab] = keyword in title or abstract

[tw] = Text word

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords
Direct crash risk	Accident Accident prevention Accidents Accidents, occupational Accidents, traffic Highway safety Motor traffic accidents Occupational health Occupational safety Safety Traffic accident Traffic safety Transportation accidents	Accident$ Citation$ Collision$ Crash$ Ticket$ Wreck$
Driving	Automobile driver examination Automobile driving Car driving Driv$.hw. Driver license Driving ability Driving behavior Drivers	Driver$ Driving[ti] Drive Highway Licens$
Motor vehicles	Automobiles Motor vehicle Motor vehicles	Bus Buses Car Cars Haul Long distance Lorry Lorries Motor$ Semi-trailer$ Truck$1 Vehicle$
Neuropsychological tests	Exp neuropsychological tests/	Aphasia Assessment$ Batter$ Evaluation Neurocog$ Neuropsych$ Test$
Risk	Proportional hazard model Proportional hazards models Exp risk/	Predict$ Risk$

Concept	Controlled Vocabulary	Keywords
Stroke	Exp brain infarction/ Exp cerebrovascular accident/ Cerebrovascular accidents Stroke	Acute focal cerebral vasculopathy Apoplexy Brain attack Brain infarct$ Brain insult Cerebral attack Cerebral infarct$ Cerebral insult CVA

CINAHL/EMBASE/MEDLINE/PsycINFO
English language, human

Set Number	Concept	Search Statement
1	Stroke	Exp cerebrovascular accident/ or exp brain infarction/ or (cerebrovascular accidents or stroke).de.
2		(Acute focal cerebral vasculopathy or apoplexy or CVA or ((brain or cerebral) adj (attack or infarct$ or insult)))
3	Combine sets	1 or 2
4	Limit by population	3 and (exp child/ or adolescent.de. or child$ or pediatr$ or paediatr$ or juvenile$ or adolescen$ or teen$ or youth$)
5		4 and adult
6		4 not 5
7		3 not 6
8	Limit by publication type	7 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
9	Accidents	8 and (accident or accidents or accidents, traffic or traffic accident or motor traffic accidents or accidents, occupational or accident prevention or occupational accident or transportation accidents).de.
10		8 and ((accident$ adj (car or traffic)) or collision$ or crash$ or wreck$ or citation$ or ticket$)
11	Driving	8 and (Automobiles or Motor vehicles or Motor vehicle or Automobile driving or Car driving or Driving ability or Driving behavior or Drivers).de.
12		8 and (driver$ or driving$ or drive or licens$ or highway$ or car or cars or vehicle$ or semi-trailer$ or bus or buses or truck$1 or lorry or lorries or haul or (long adj distance)).ti.
13		8 and (Automobile driver examination or Licensure or Driver license or Safety or Traffic safety or Highway safety or Occupational safety or Occupational Health or Occupational disease).de.
14	Combine sets	or/9-13
15	Eliminate overlap	Remove duplicates from 14
16	Limit by study type	15 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebos or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or Case control studies/ or Cohort/ or Longitudinal studies/ or Evaluation studies/ or Follow-up studies/ or Prospective studies/ or Retrospective studies/ or Case control study/ or Cohort analysis/ or Longitudinal study/ or Follow up/ or Cohort analysis/ or Followup studies/ or random$.hw. or random$.ti. or placebo$.mp. or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham or mask)).mp. or latin square.mp. or (time adj series) or (case adj (study or studies) or ISRCTN$.mp. or ACTRN$.mp. or (NCT$ not nctc$)))
17		15 and (driving.ti. or driv$.hw.)

Set Number	Concept	Search Statement
18	Combine sets	16 or 17
19	Neuropsychological assessment	15 and (exp neuropsychological tests/ or ((neuropsych$ or neurocog$ or aphasia) and (test$ or assessment$ or evaluation or batter$)))

Total Identified	Total Downloaded	Total Retrieved	Total Included
1,152	**96**	**31**	**18**

Search summary for Key Question 3

The search strategies employed combinations of free text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts: accidents, mental disorders, mental disease, driving, and motor vehicle operation. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE, MEDLINE, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

Transient Ischemic Attack

Electronic Database Searches

The following databases have been searched for relevant information.

Name	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 through January 10, 2008	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2007, Issue 4	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2007, Issue 4	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2007, Issue 4	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2007, Issue 4	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through January 10, 2008	OVID
MEDLINE	1950 through January 10, 2008	OVID
PreMEDLINE	Searched January 10, 2008	OVID
PsycINFO	Through January 10, 2008	OVID
TRIS	Searched December 18, 2007	

Name	Date Limits	Platform/Provider
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2007, Issue 4	www.thecochranelibrary.com

Medical Subject Headings (MeSH), EMTREE, PsycINFO and Keywords

Conventions:

OVID

$ = truncation character (wildcard)

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication Type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = Publication Type

[sb] = Subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)

[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)

[tiab] = keyword in title or abstract

[tw] = Text word

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords
Direct crash risk	Accident Accident prevention Accidents Accidents, occupational Accidents, traffic	Accident$ Citation$ Collision$ Crash$ Ticket$

Concept	Controlled Vocabulary	Keywords
	Highway safety Motor traffic accidents Occupational health Occupational safety Safety Traffic accident Traffic safety Transportation accidents	Wreck$
Driving	Automobile driver examination Automobile driving Car driving Driv$.hw. Driver license Driving ability Driving behavior Drivers	Driver$ Driving[ti] Drive Highway Licens$
Motor vehicles	Automobiles Motor vehicle Motor vehicles	Bus Buses Car Cars Haul Long distance Lorry Lorries Motor$ Semi-trailer$ Truck$1 Vehicle$
Risk	Proportional hazard model Proportional hazards models Exp risk/	Predict$ Risk$
Stroke	Exp brain infarction/ Exp cerebrovascular accident/ Cerebrovascular accidents Stroke	Acute focal cerebral vasculopathy Apoplexy Brain attack Brain infarct$ Brain insult Cerebral attack Cerebral infarct$ Cerebral insult CVA
Transient ischemic attack	Ischemic attack, transient Transient ischemic attack	TIA Transient adj ischem$

CINAHL/EMBASE/MEDLINE/PsycINFO

English language, human

Set Number	Concept	Search Statement
1	TIA	(Ischemic attack, transient or transient ischemic attack).de.
2		TIA or (transient adj ischem$)

Set Number	Concept	Search Statement
3	Combine sets	1 or 2
4	Stroke	Exp cerebrovascular accident/ or exp brain infarction/ or (cerebrovascular accidents or stroke).de.
5		(Acute focal cerebral vasculopathy or apoplexy or CVA or ((brain or cerebral) adj (attack or infarct$ or insult)))
6	Combine sets	4 or 5
7	Risk	Exp risk/ or risk$.ti. or proportional hazard models.de. or proportional hazards model.de.
8	Combine sets	3 and 6 and 7
9	Limit by population	8 and (exp child/ or adolescent.de. or child$ or pediatr$ or paediatr$ or juvenile$ or adolescen$ or teen$ or youth$)
10		9 and adult
11		9 not 10
12		8 not 11
13	Limit by publication type	12 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
14	Eliminate overlap	Remove duplicates from 13
15	Limit by study type	14 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebos or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or Case control studies/ or Cohort/ or Longitudinal studies/ or Evaluation studies/ or Follow-up studies/ or Prospective studies/ or Retrospective studies/ or Case control study/ or Cohort analysis/ or Longitudinal study/ or Follow up/ or Cohort analysis/ or Followup studies/ or random$.hw. or random$.ti. or placebo$.mp. or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham or mask)).mp. or latin square.mp. or (time adj series) or (case adj (study or studies) or ISRCTN$.mp. or ACTRN$.mp. or (NCT$ not nctc$)))
17		16 and (risk$ or predict$)
18		16 and (risk$ or predict$).ti.

Total Identified	Total Downloaded	Total Retrieved	Total Included
553	**98**	**113**	**13**

Appendix B: Retrieval Criteria

Listed below are the retrieval criteria, the criteria that each identified abstract had to satisfy in order to be retrieved in full.

Retrieval Criteria for Key Question 1

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash directly (risk for a fatal or nonfatal crash) associated with stroke.
    - Reporting direct evidence of crash risk
    - Reporting evidence of driver safety through driving tests or simulation
- Article must describe a study that includes a comparison group comprised of comparable subjects who had not had a stroke.

Retrieval Criteria for Key Question 2

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the association between risk for a motor vehicle crash in stroke patients and neuropsychological test scores
- Included patients must have had a stroke.

Retrieval Criteria for Key Question 3

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk of stroke following a TIA or attempted to determine the prevalence of TIA in subjects who experienced a stroke.
- Article must describe a study that includes a comparison group comprised of comparable subjects who did not have a TIA or a comparison group comprised of comparable subjects who did not experience a stroke.

Appendix C: Inclusion Criteria

Listed below are the inclusion criteria for each of the seven key questions addressed in this evidence report. These are the criteria that had to be satisfied in order for an article to be included in the evidence base.

Inclusion Criteria for All Key Questions

- Article must have been published in the English language. Moher et al.(182) have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn. Juni et al.(183) found that non-English studies typically were of lower methodological quality and that excluding them had little effect on effect size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary for translation of studies to identify those of acceptable quality for inclusion in our reviews.(182,183)
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects per group
- Article must have enrolled subjects aged ≥18.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted to avoid double-counting individuals.

Additional Criterion for Key Question 1

- Article may describe a study that attempted to evaluate the relationship between people who have had a stroke and the following direct and indirect measures of driver safety:
    - Direct evidence of crash risk
    - Measures of driving-related performance (laboratory and experimental)

Additional Criterion for Key Question 2

- Article may describe a study that attempted to evaluate the relationship between neuropsychological testing scores and crash incidence or driving performance in drivers who have had a stroke.

Additional Criteria for Key Question 3

- Studies were limited to individuals with TIA only (no reversible ischemic attacks or reversible ischemic neurologic deficits).
- Studies that evaluated both TIA and other neurologic deficits were included as long as data for TIA subjects could be analyzed separately from that of other subject populations.
- Article must describe a study that attempted to directly determine the risk of stroke associated with TIA or attempted to determine the prevalence of TIA in subjects who had a stroke.
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have TIA or includes a comparison group comprised of comparable subjects who did not have a stroke.

Appendix D: Excluded Articles

Table D-1. Excluded studies (Key Question 1)

Reference	Year	Reason for Exclusion
Akinwuntan et al.(184)	2005	No control group or reference standard
Akinwuntan et al.(149)	2002	No control group or reference standard
Akinwuntan et al.(185)	2005	No control group or reference standard
Fisk et al.(186)	2002	No relevant outcomes reported
George et al.(187)	2007	Data not reported separately for control group
Huchler et al.(188)	2001	No control group or reference standard, stroke patients not reported on separately from people with other diagnoses
Keller et al.(189)	2003	No control group or reference standard
Kizony and Katz(190)	2002	No relevant outcomes reported
Klavora et al.(191)	2000	No control group or reference standard
Klavora et al.(192)	1994	No control group or reference standard
Lee et al.(193)	2003	No relevant outcomes reported
Legh-Smith et al.(194)	1986	No relevant outcomes reported
Lundqvist(195)	2001	No control group or reference standard
Mackenzie and Paton(196)	2003	No relevant outcome reported
Mazer et al.(197)	2001	No relevant outcomes reported
Mazer et al.(198)	2003	No control group or reference standard
Nouri et al.(154)	1987	No control group or reference standard
Nouri and Lincoln(153)	1992	No control group or reference standard
Nouri and Lincoln(152)	1993	No control group or reference standard
Patomella et al.(199)	2006	No control group or reference standard
Quigley et al.(200)	1983	No control group or reference standard
Schultheis et al.(201)	2007	No relevant outcomes reported
Sentinella et al.(202)	2005	No relevant outcomes reported
Smith-Arena et al.(147)	2005	No control group or reference standard
Soderstrom et al.(99)	2006	No control group or reference standard
Stewart et al.(203)	1993	No control group or reference standard

Table D-2. Excluded studies (Key Question 2)

Reference	Year	Reason for Exclusion
Innes et al.(204)	2007	Mixes patients with stroke and patients with other brain disorders
Patomella et al.(199)	2006	No neuropsychological tests used
Schanke and Sundet(205)	2000	Mixes patients with stroke and patients with other neurologic disorders
Klavora et al.(191)	1995	Rehabilitation of people who failed driving tests, not a study of neuropsychological tests to predict driving test outcomes
Fox et al.(206)	1992	Patients who failed neuropsychological tests were not allowed to take driving test, so predictive value of neurological tests on driving test outcome cannot be determined.

Table D-3. Excluded Studies (Key Question 3)

Reference	Year	Reason for Exclusion
Boulanger et al.(207)	2007	No control group
Bray et al.(208)	2007	No control group
Byrne et al.(209)	2007	Evaluates ABCD scoring system for predicting stroke
Hankey GJ.(210)	2007	Abstract and Commentary
Jamieson DG.(211)	2007	Review
Johnston et al.(212)	2007	Evaluates scoring system for predicting stroke
Lin et al.(213)	2007	No control group
Maasland et al.(214)	2007	Does not report risk of stroke following a TIA
No Author Listed(215)	2007	Review
Purroy et al.(216)	2007	No control group
The Stroke Risk in Atrial Fibrillation Working Group(217)	2007	Systematic review of independent predictors of stroke in individuals with atrial fibrillation
Sylaja and Hill(156)	2007	Review
Tsivgoulis et al.(218)	2007	Review
Acciarresi et al.(219)	2006	Does not report risk of stroke following a TIA
Ariesen et al.(220)	2006	Does not report whether all individuals in the study had TIA
Ay and Koroshetz(221)	2006	Review
Bernstein et al.(222)	2006	Review
Bhatia et al.(223)	2006	Includes same individuals as Clark et al., 2003(224)
Boulanger et al.(225)	2006	Study group includes individuals with TIA and stroke, but TIA is not reported separately
Correia et al.(226)	2006	No control group
Cucchiara et al.(227)	2006	Evaluates ABCD scoring system for predicting stroke
Flossmann and Rothwell(228)	2006	Evaluates whether family history of stroke predicts risk of stroke following a TIA
Giles and Rothwell(158)	2006	Review
Halkes et al.(229)	2006	Study group includes individuals with TIA and stroke, but TIA is not reported separately
Hart R.(230)	2006	Abstract and Commentary
Howard et al.(231)	2006	Does not report risk of stroke following a TIA

Reference	Year	Reason for Exclusion
Kang et al.(232)	2006	Does not report risk of stroke following a TIA
Somay et al.(233)	2006	Does not report risk of stroke following a TIA
Tsivgoulis et al.(234)	2006	No control group
Vermeer et al.(235)	2006	Study group includes individuals with TIA and stroke, but TIA is not reported separately
Bos et al.(236)	2005	Study group includes individuals with TIA and stroke, but TIA is not reported separately
Brown et al.(237)	2005	Study group includes individuals with TIA and stroke, but TIA is not reported separately
Carciumaru and Damian(238)	2005	No control group
Kleindorfer et al.(16)	2005	No control group
Nguyen-Huynh and Johnston(160)	2005	Review
No Author Listed(239)	2005	Review
Pantoni et al.(240)	2005	No control group
Rothwell et al.(241)	2005	Evaluates ABCD scoring system for predicting stroke
Van Wijk et al.(242)	2005	Study group includes individuals with TIA and stroke, but TIA is not reported separately
Woodward et al.(243)	2005	Does not report risk of stroke following a TIA
Coull et al.(244)	2004	No control group
Daffertshofer et al.(245)	2004	No control group
Eliasziw et al.(246)	2004	No control group
Gladstone et al.(247)	2004	No control group
Hardie et al.(248)	2004	Study group consisted of individuals with stroke
Hart et al.(249)	2004	Evaluates treatments for TIA
Herve et al.(250)	2004	Does not report risk of stroke following a TIA
Hill et al.(15)	2004	No control group
Lisabeth et al.(251)	2004	No control group
Rothwell et al.(252)	2004	Evaluates incidence of stroke
Appelros et al.(253)	2003	Evaluates the risk of stroke following a first ever stroke
Arenillas et al.(254)	2003	Study group includes individuals with TIA and stroke, but TIA is not reported separately
Clark et al.(224)	2003	Unable to determine follow-up time with the data reported
Douglas et al.(255)	2003	Study group consists of the same individuals as in Johnston et al., 2000(46)
Johnston et al.(256)	2003	Study group consists of the same individuals as in Johnston et al., 2000(46)
Johnston et al.(257)	2003	Does not report risk of stroke following a TIA
Johnston et al.(13)	2003	Does not evaluate risk of stroke following a TIA
Lovette et al.(258)	2003	No control group
Rothwell PM.(159)	2003	Review
Bushnell CD.(259)	2002	Does not report risk of stroke following a TIA
Garcia-Monco et al.(260)	2002	Evaluates TIA-mimicking conditions
Johnsen et al.(261)	2002	Does not report risk of stroke following a TIA
Mead et al.(262)	2002	Does not report risk of stroke following a TIA

Reference	Year	Reason for Exclusion
Lee et al.(263)	2001	Does not report risk of stroke following a TIA
Arboix et al.(264)	2000	Does not report risk of stroke following a TIA
Cote et al.(265)	2000	No control group
Johnston et al.(46)	2000	No control group
Kernan et al.(266)	2000	Evaluates The Stroke Prognosis Instrument II (SPI-II)
Whisnant et al.(267)	1999	Does not report incidence of stroke in TIA group
Hankey et al.(268)	1998	Evaluates the risk of stroke following a first-ever stroke
Puranen et al.(269)	1998	Evaluates the effectiveness of antiplatlet therapy
Valton et al.(270)	1998	Not all individuals included in the study group had TIA
Bots et al.(271)	1997	Does not report risk of stroke following a TIA
Dippel and Koudstaal(272)	1997	Study group includes individuals with amaurosis fugax and nondisabling stroke
Jorgensen et al.(273)	1997	Evaluates the risk of stroke following a first-ever stroke
Valton et al.(274)	1997	Does not report risk of stroke following a TIA
Donnan et al.(275)	1996	No control group
Henriques et al.(276)	1996	Does not report risk of stroke following a TIA
Streifler et al.(277)	1995	Study group consists of individuals with high-grade carotid stenosis, and are therefore at higher risk of stroke than general population
Van Latum et al.(278)	1995	Does not report risk of stroke following a TIA
Burn et al.(279)	1994	Study group consisted of individuals with stroke
Comess et al.(280)	1994	Study group includes individuals with TIA and stroke, but TIA is not reported separately
Lai et al.(281)	1994	Does not report risk of stroke following a TIA
Pop et al.(282)	1994	Does not report risk of stroke following a TIA
Davalos A.(283)	1993	Letter to the editor
The Dutch TIA Trial Study Group(284)	1993	Does not report risk of stroke following a TIA
Hankey et al.(285)	1993	Reports risk of “stroke, myocardial infarction or vascular death” following a TIA
Sarker et al.(286)	1993	Does not report risk of stroke following a TIA
Hankey et al.(287)	1992	Includes same individuals as Hankey et al., 1991(288)
Koudstaal et al.(289)	1992	Study group includes individuals with TIA and stroke, but TIA is not reported separately
Levine et al.(290)	1992	Study group includes individuals with TIA and stroke, but TIA is not reported separately
Hankey et al.(288)	1991	No control group
Li et al.(291)	1990	Unable to determine effect size from reported data
Spriggs et al.(292)	1990	Does not report risk of stroke following a TIA
Sobel et al.(293)	1989	Evaluates risk factors for recurrent stroke following a stroke
Alter et al.(294)	1987	Evaluates risk factors for recurrent stroke following a stroke
Ueda et al.(295)	1987	Evaluated only a subset of strokes that occurred in the population
Calandre and Molina(296)	1985	No control group
Haberman S.(157)	1984	Systematic review that evaluates mortality following a TIA
Heyman et al.(297)	1984	No control group

Reference	Year	Reason for Exclusion
Muuronen and Kaste(298)	1982	No control group
Simonsen et al.(299)	1981	Does not report risk of stroke following a TIA
Terent A.(300)	1979	Does not report risk of stroke following a TIA
Cartlidge et al.(301)	1977	Included some of the same individuals as in Whisnant et al., 1973(173)
Karp et al.(302)	1973	Evaluates prevalence of TIA in community.
Acheson and Hutchinson(303)	1971	Evaluates individuals with cerebral vascular insufficiency
Goldner et al.(304)	1971	No control group
Friedman et al.(305)	1969	No control group
Baker et al.(306)	1968	No control group
Siekert et al.(307)	1963	May have included some of the same individuals as in Whisnant et al., 1973(173)
McDowll et al.(308)	1961	Does not report risk of stroke following a TIA
David and Heyman(309)	1960	Does not report risk of stroke following a TIA
Lindgren SO(310)	1958	Does not report risk of stroke following a TIA

TIA = Transient Iscemic Attack

Appendix E: Determining the Stability and Strength of a Body of Evidence

As stated in the main text, ECRI evidence reports differ substantially from other systematic reviews in that we provide two types of conclusion; qualitative conclusions and quantitative conclusions. In order to reach these conclusions we use an algorithm developed by ECRI to guide the conduct and interpretation of the analyses performed during the development of this evidence report.(100) The algorithm, which is presented in Figure E-2 through Figure E-5, formalizes the process of systematic review by breaking the process down into several discrete steps. At each step, rules are applied that determine the next step in the systematic review process and ultimately to the stability and strength of evidence ratings that are allocated to our conclusions. Because the application of the rules governing each step in the algorithm (henceforth called a decision point) guide the conduct of the systematic review process and how its findings are interpreted, much time and effort was spent in ensuring that the rules and underlying assumptions for each decision point were reasonable.

The algorithm is comprised of three distinct sections: a *General* section, a *Quantitative* section, and a *Qualitative* section. The system employs 14 decision points (Table 44). Four of them are listed in the General section because they apply to both quantitative conclusions as well as qualitative conclusions. The other 10 apply specifically to either quantitative conclusions (Decision Points 5-9) or qualitative conclusions (Decision Points 10-14). The rest of this appendix defines these decision points and describes how we resolved them for this report. After these descriptions, the pathways for the full system appear in Figure E-2 through Figure E-5.

Note that we applied this system separately for each outcome of interest. This is because many aspects of the evidence (quality, consistency, etc.) can vary by outcome.

Table 44. Decision Points in the ECRI System

Category	Decision Point
General	1) What is the quality of individual studies?
	2) What is the overall quality of evidence?
	3) Is a quantitative estimate potentially appropriate?
	4) Are data informative?
Quantitative	5) Are data quantitatively consistent (homogeneous)?
	6) Are findings stable (quantitatively robust)?
	7) Are there sufficient data to perform meta-regression?
	8) Does meta-regression explain heterogeneity?
	9) Is the meta-regression model robust?
Qualitative	10) Are data qualitatively robust?
	11) Is meta-analysis possible?
	12) Are data qualitatively consistent?

Category	Decision Point
	13) Was at least one study a multicenter study?
	14) Is the magnitude of effect extremely large?

Decision Point 1: Acceptable Quality?

Decision Point 1 serves two purposes: 1) to assess the quality of each included study; 2) to provide a means of excluding studies that are so prone to bias that their reported results cannot be considered useful. To aid in assessing the quality of each of the studies included in this evidence report, we used two study quality assessment instruments. The choice of which instrument to use was based on the design of the study used to address the key questions of interest. In this evidence report we used two revised versions of the Newcastle-Ottawa Quality Assessment Scale (one for case-control studies, one for cohort studies).(311) These instruments are presented in Appendix F. To assess the quality of an individual study, we computed a normalized score so that a perfect study received a score of 10, a study for which the answers to all items was "No" received a score of 0, and a study for which the answers to all questions was "NR" was 5. Quality scores were converted to categories as shown in Table X (see Methods section of main document). The definitions for what constitutes low, moderate, or high quality evidence were determined *a priori* by a committee of four methodologists. Because the quality was determined separately for each outcome, a study that scored as high quality for one outcome might score as moderate or low quality for another outcome.

Decision Point 2: Determine Quality of Evidence Base

We classified the overall quality of each key question's specific evidence base into one of three distinct categories; high, moderate or low quality. Decisions about the quality of each evidence base were based on data obtained using the quality assessment instruments described above using the criteria presented in Table E-1.

Table E-1. Criteria Used to Categorize Quality of Evidence Base

Category	Median NOQAS Score (case-control)	Median NOQAS Score (cohort)
High Quality		
Moderate Quality	≥8.0	≥8.0
Low Quality	<8.0	<8.0

Decision Point 3: Is a Quantitative Analysis Potentially Appropriate?

The answer to Decision Point 3 depends upon the adequacy of reporting in available studies as well as the number of available studies. In order to permit a quantitative estimate of an effect size for a given outcome, the data for that outcome must be reported in at least three studies in a manner that allows the data to be pooled in a meta-analysis. If less than three studies are available, no quantitative estimate is usually appropriate, regardless of reporting. Another

situation that does not permit a quantitative estimate is when at least three studies are relevant to the general topic, but fewer than 75% of them reported the outcome as well as sufficient information for determination of the effect size and its dispersion, either by direct reporting from the trial or calculations based on reported information. If no quantitative estimate would be appropriate, then one moves directly to Decision Point 10 to determine whether the evidence supports a qualitative conclusion.

Decision Point 4: Are Data Informative?

When there are only a small number of patients in an evidence base, statistical tests generally do not perform well. Under such circumstances, statistics cannot determine whether a true difference exists between treatments. This means that no clear conclusion can be drawn. For this decision point, we determined whether the precision of an evidence base was sufficient to permit a conclusion. Statistically significant results are informative because they mean that a treatment effect may exist. Statistically non-significant results are also potentially informative, but only if they exclude the possibility that a clinically significant treatment effect exists.

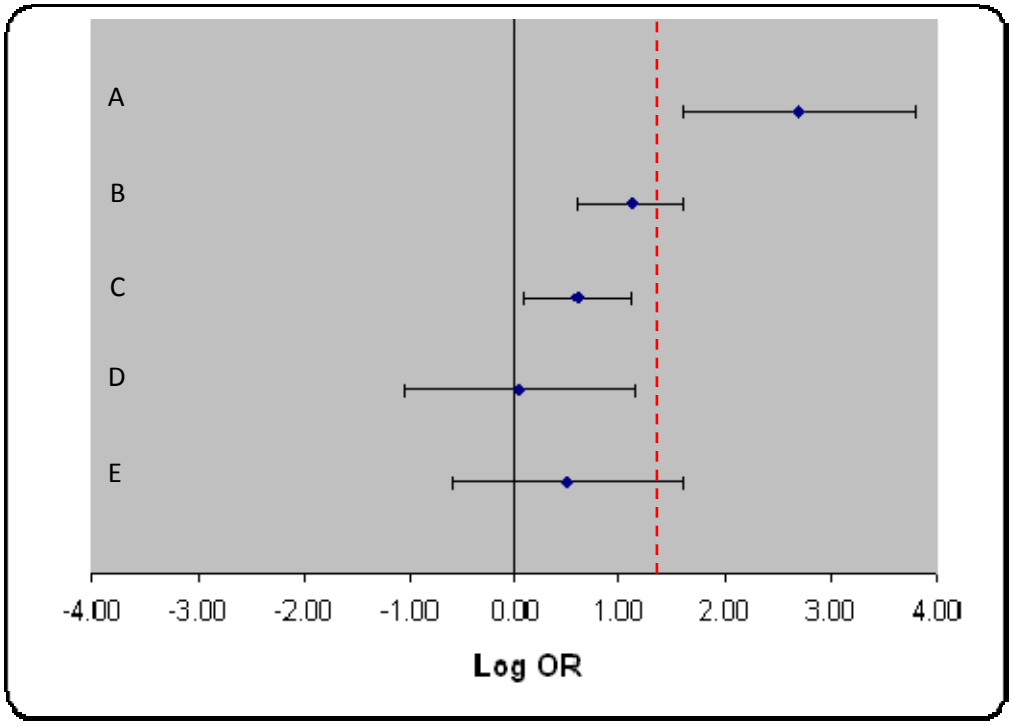
When a meta-analysis is performed, a key concern is the confidence interval around the random-effects summary statistic. If this interval is so wide that it is includes a clinically significant (or substantial) effect in one direction *and also an effect in the opposite direction*, then the evidence is inconclusive, and therefore uninformative.(312)

Thus, when considering the summary effect size from a meta-analysis (or the effect size from a single study), there are three ways in which the effect can be "informative":

1) The effect size is statistically significantly different from 0. This would be indicated whenever the confidence interval does not overlap 0.
2) The confidence interval is narrow enough to exclude the possibility that a *clinically significant difference* exists.
3) The confidence interval is narrow enough to exclude the possibility that a *substantial difference* exists. This possibility is included to address situations when even a very small effect can be considered "clinically significant" (e.g., a difference in mortality rates), but the effect may not be "substantial".

Consider Figure E-1. Four of the findings in this figure are informative (A to D). Only finding E is non-informative.

Figure E-1. Informative Findings



Dashed Line = Threshold for a clinically significant difference

Finding A shows that the treatment effect is statistically significant and clinically important. Finding B shows that the treatment effect is statistically significant but it is unclear whether this treatment effect is clinically important. Finding C shows that the treatment effect is statistically significant but that the treatment effect is too small to be considered clinically important. Finding D shows that it is unclear whether there is a statistically important treatment effect, but regardless, this treatment effect is not clinically important. Finding E shows that it is unclear whether there is a statistically important treatment effect and it is also unclear whether the treatment effect is clinically important. This latter finding is thus non-informative.

Note that when the evidence base consists of one or two studies, and the only usable data from one study consists of a p-value that was calculated using the wrong statistical test, then the data cannot generally be considered "informative." If, however, the study reported sufficient information for one to perform the correct test, then informativeness can be determined.

Decision Point 5: Are Data Quantitatively Consistent (Homogeneous)?

This decision point was used only when the answer to Decision Point 3 was affirmative and a quantitative analysis was performed. Quantitative consistency refers to the extent to which the quantitative results of different studies are in agreement. The more consistent the evidence, the more precise a summary estimate of treatment effect derived from an evidence base will be. Quantitative consistency refers to consistency tested in a meta-analysis using a test of

homogeneity. For this evidence report we used Higgins and Thompson's I^2 statistic.(113) By convention, we considered an evidence base as being quantitatively consistent when I^2 <50%.

If the findings of the studies included were homogeneous (I^2 <50%), we obtained a summary effect size estimate by pooling the results of these studies using random-effects meta-analysis (REMA). If the findings were not homogeneous, we moved on to Decision Point 7 (exploration of heterogeneity, if ≥10 studies) or Decision Point 9 (qualitative analysis).

Decision Point 6: Are Findings Stable (Quantitatively Robust)?

If the findings of the random-effects meta-analysis were found to be homogeneous, we next assessed the stability of the summary effect size estimate obtained. Stability refers to the likelihood that a summary effect estimate will be substantially altered by changing the underlying assumptions of the analysis. Analyses that are used to test the stability of an effect size estimate are known as sensitivity analyses. Clearly, ones confidence in the validity of a treatment effect estimate will be greater if sensitivity analyses fail to significantly alter the summary estimate of treatment effect.

For this evidence report, we utilized three different sensitivity analyses. These sensitivity analyses are:

1. *Removal of one study and repeat meta-analysis.* The purpose of this sensitivity analysis is to determine whether a meta-analysis result is driven by a particular trial. For example, a large trial may have a very strong impact on the results of a meta-analysis because of its high weighting.
2. *Publication bias test.* The publication bias test used in this evidence report was that of Duval and Tweedie.(127-129,313)Based on the degree of asymmetry in a funnel plot constructed from the findings of the included studies, this test(128,129)estimates the number of unpublished studies (and their effect sizes). After addition of any "missing" data to the original meta-analysis, the overall effect size is estimated again. If evidence of publication bias was identified and the summary effect size estimate, adjusted for "missing" studies, differed from the pooled estimate of treatment effect determined by the original fixed-effects meta-analysis by >±5%, we determined that the findings of our original analysis are not robust and the effect size estimate is not stable.
3. *Cumulative random-effects meta-analysis.* Cumulative meta-analysis provides a means by which one can evaluate the effect of the size of the evidence base (in terms of the number of individuals enrolled in the included studies and the number of included studies) on the stability of the calculated effect size estimate. For this evidence report, we performed two different cumulative random-effects meta-analyses:
    a. Studies were added cumulatively to a random-effects meta-analysis by date of publication-oldest study first.

b. Studies were added cumulatively to a random-effects meta-analysis by date-newest study first.

In each instance, the pooled effect size estimate was considered unstable if any of the last three studies to be added resulted in a change in the cumulative summary effect size estimate effect of >±5%.

The prespecified tolerance levels for each of the potential effect size estimates we could have utilized in this evidence report are presented in Table E-2.

Table E-2. Prespecified Tolerance Levels

Effect size estimate	WMD	SMD	% of individuals	RR	OR
Tolerance	+/-5%	+/-0.1	+/-5%	+/-0.05	+/-0.05

Decision Point 7: Are There Sufficient Data to Perform Meta-Regression?

We required a minimum of 10 studies before attempting meta-regression.

Decision Points 8 and 9: Exploration of Heterogeneity

We will always attempt to determine the source of heterogeneity when the evidence base consists of 10 or more studies using meta-regression. In preparing this evidence report we did not encounter any situations where we had a heterogeneous evidence base consisting of at least 10 studies. Consequently, Decision Points 8 and 9 are irrelevant to the present report and we do not discuss them further.

Decision Point 10: Are Qualitative Findings Robust?

Decision Point 10 allows one to determine whether the qualitative findings of two or more studies can be overturned by sensitivity analysis. The same sensitivity analyses used to test quantitative robustness were used to test qualitative robustness. We considered our qualitative findings to be overturned only when the sensitivity analyses altered our qualitative conclusion (i.e., a statistically significant finding became non-significant as studies were added to the evidence base). Otherwise, we concluded that our qualitative findings were robust.

Decision Point 11: Is Meta-analysis Possible?

This Decision Point is used only when the evidence base for an outcome consists of two studies.

A meta-analysis is possible if each study reports an effect size and its standard error, or if each study reports sufficient information for the reader to calculate these values. Note that meta-analysis is never appropriate if two studies have statistically significant effect sizes in opposite directions.

Decision Point 12: Are Data Qualitatively Consistent?

This Decision Point is used only when the evidence base for an outcome consists of two studies.

The purpose of this decision point is to determine whether the qualitative findings of an evidence base consisting of only two studies are the same. For example one might ask, "When compared to healthy controls, do all included studies find that stroke is a significant risk factor for a motor vehicle crash?"

Decision Point 13: Is at Least One Study a Multicenter Study?

Multicenter trials may increase the strength of a one or two-study evidence base because they demonstrate partial replication of findings; they have shown that different investigators at different centers can obtain similar results using the same protocol. We defined a multicenter trial as any trial that met the following two conditions: 1) ≥3 centers and 2) either ≥100 patients or at least 3 centers enrolled ≥20 patients/center.

Decision Point 14: Is Magnitude of Treatment Effect Large?

When considering the strength of evidence supporting a qualitative conclusion based on only one or two studies, magnitude of effect becomes very important. The more positive the findings, the more confident one can be that new evidence will not overturn ones qualitative conclusion.

The algorithm divides the magnitude of effect into two categories–large and not large. Determining the threshold above which the observed magnitude of effect can be considered to be "large" cannot usually be determined *a priori*. In cases where it is necessary to make judgments about whether an estimate of treatment effect is extremely large, the project director will present data from the two studies to a committee of three methodologists who will determine whether an effect size estimate is "extremely large" using a modified Delphi technique.

Additional Consideration: Evidence from Indirect or Surrogate Outcomes

In certain instances when an evidence base includes only one or two studies with direct evidence (e.g., crash data), the strength of evidence may be increased by additional studies of indirect outcomes (e.g., driving simulator tests, visual function tests) that show findings consistent with the direct evidence study findings.

Figure E-2. General Section

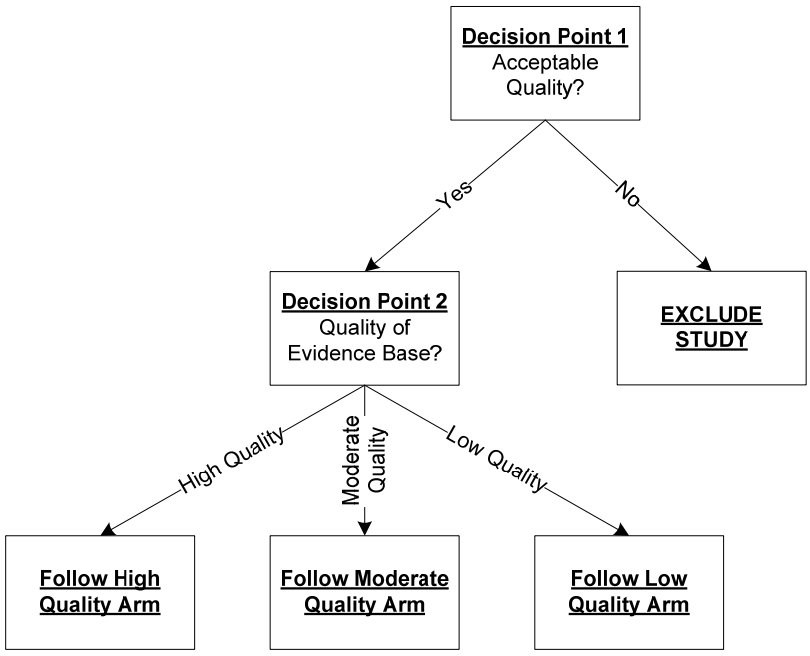


Figure E-3. High Quality Pathway

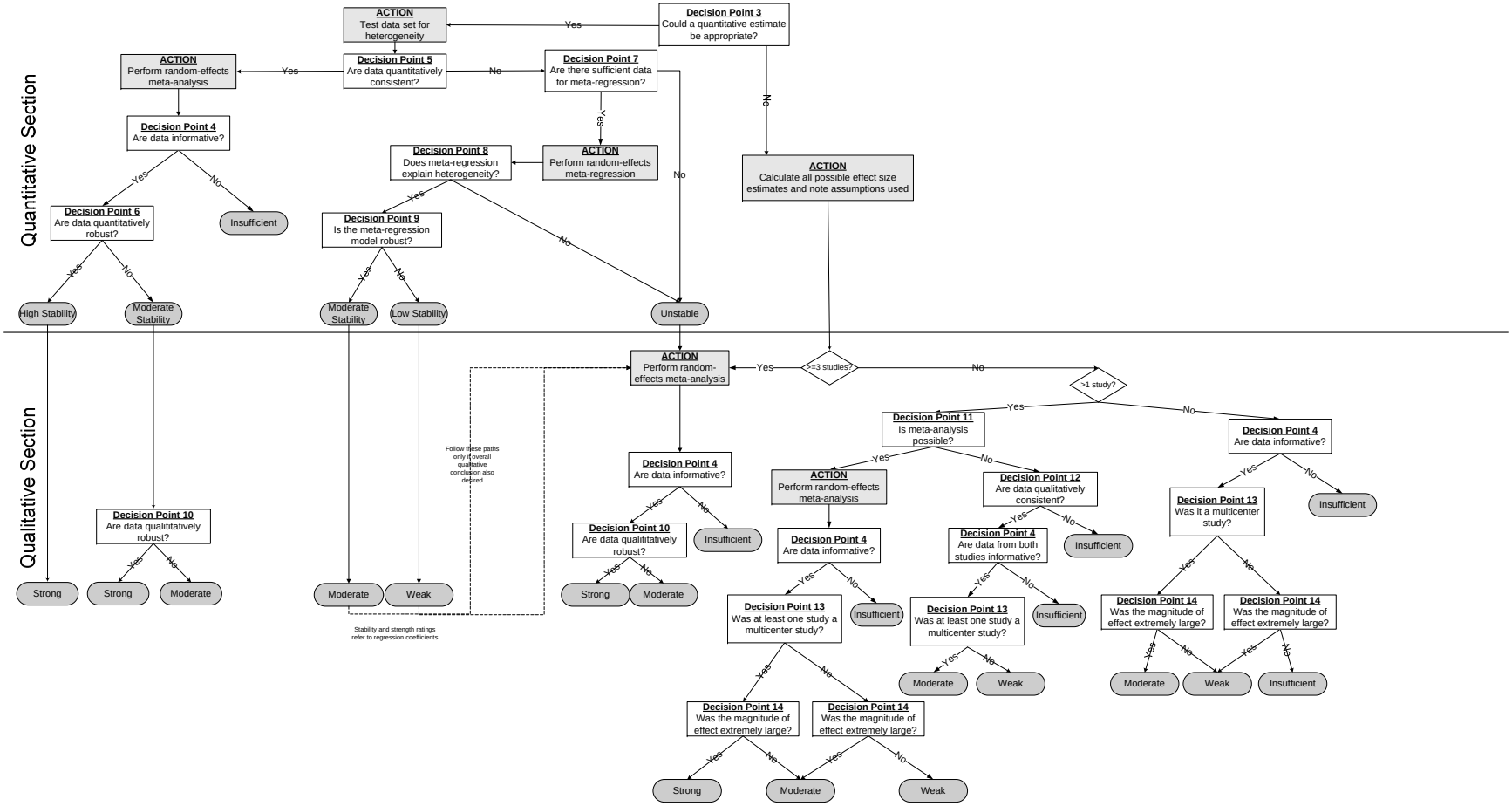


Figure E-4. Moderate Quality Pathway

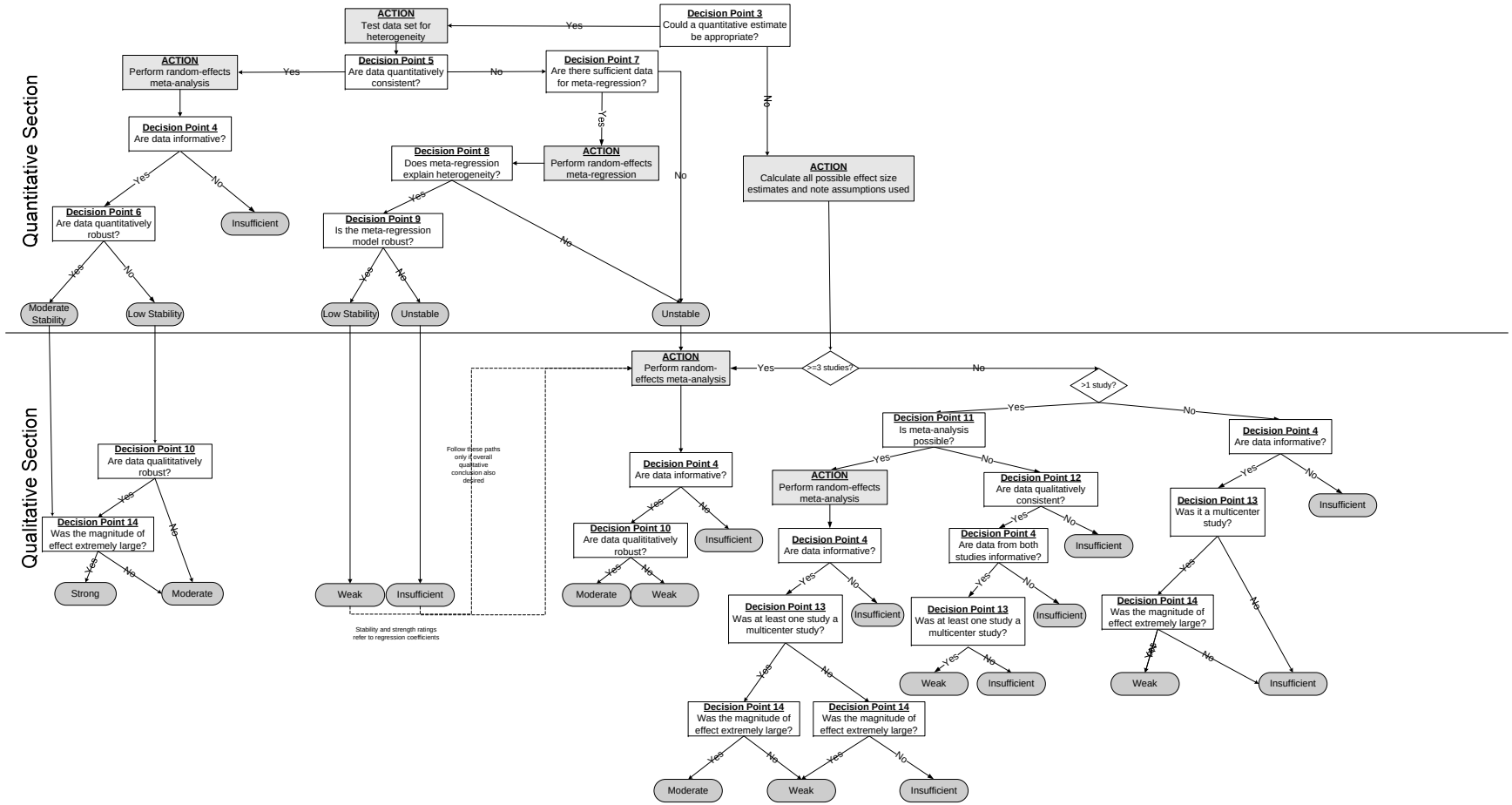
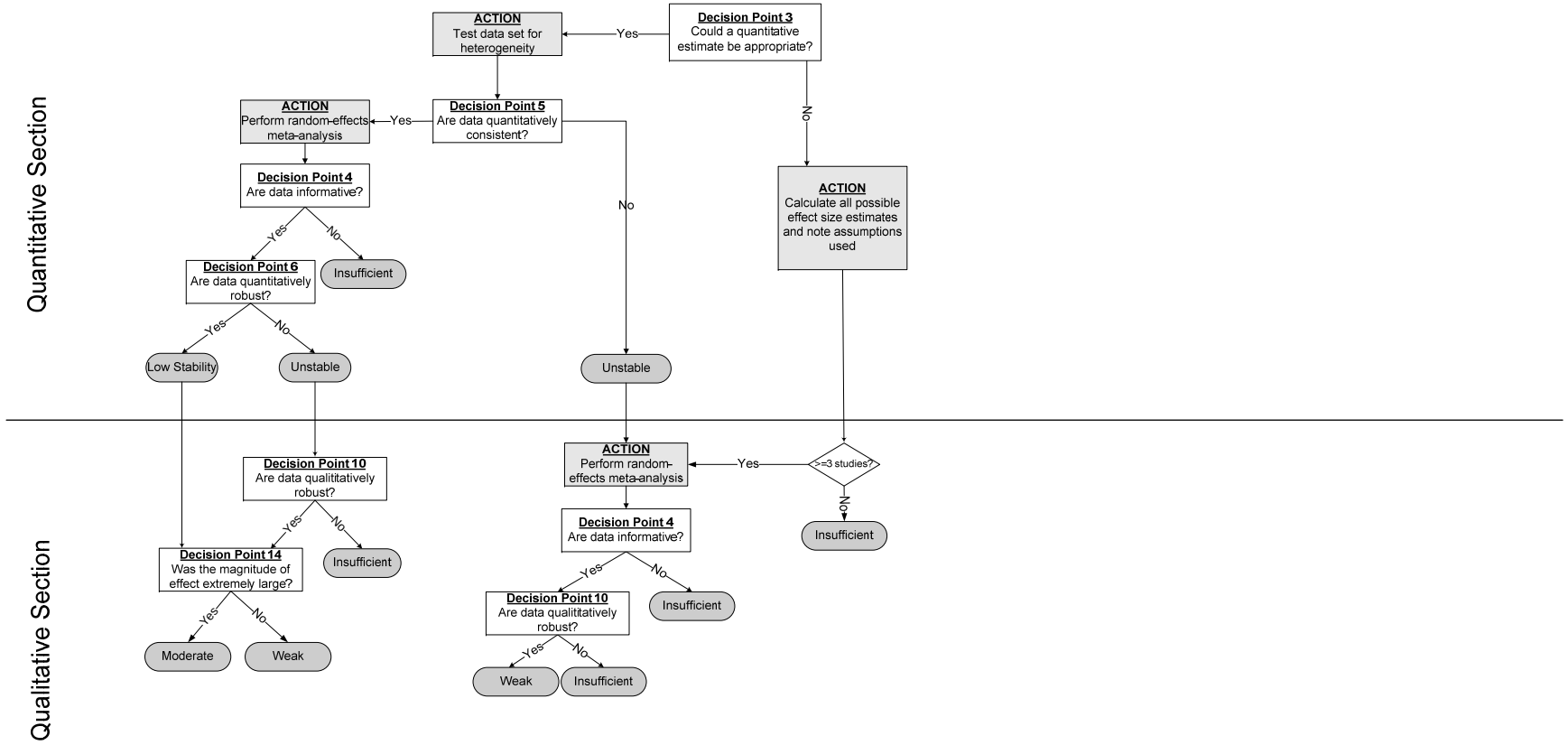


Figure E-5. Low Quality Pathway



Appendix F: Quality Assessment Instruments Used

Two different assessment instruments were used to assess the quality of the studies included in the evidence bases for the key questions addressed in this evidence report; they are revised versions of the Newcastle-Ottawa Quality Assessment Scales for Cohort Studies and Case-Control Studies.(311)

Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

Question #	Question
1	Are the exposed cohorts representative of the average motor vehicle driver in the community?
2	Are the non-exposed cohorts representative?
3	How was exposure determined – secure record?
4	At the designated start of the study, were the controls free of the outcome of interest?
5	What is the comparability of the cohorts on the basis of design or analysis?
6	How was the outcome assessed?
7	Was follow-up adequate for outcome to occur?
8	Was the follow-up adequate for both exposed and non-exposed cohorts?
9	Was the funding free of financial interest?
10	Were the conclusions supported by the data

Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies

The original Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies consisted of ten questions. We adapted the instrument to better capture some sources of bias that were not considered in the original 10-item scale.

Question #	Question
1	Do the cases have independent validation?
2	Are the cases representative?
3	Are the controls derived from the community?
4	At the designated endpoint of the study, do the controls have the outcome of interest?
5	Does the study control for the most important confounder?
6	Does the study control for any additional confounders?
7	Was exposure/outcome ascertained through a secure record (surgical, etc.)
8	Was the investigator who assessed exposure/outcome blinded to group patient assignment?
9	Was the same method of exposure/outcome ascertainment used for both groups?
10	Was the non-response rate of both groups the same?
11	Was the investigation time of the study the same for both groups?
12	Was the funding free of financial interest?
13	Were the conclusions supported by the data?

Appendix G: Quality Score Tables

Key Question 1 Cohort Study Quality Assessments

Reference	Items										Quality Category
	1	2	3	4	5	6	7	8	9	10	
Haselkorn et al. 1998(138)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Low
Sims et al. 2000(137)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Lings and Jensen 1991(141)	No	S	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Low
Lundqvist et al. 2000(142)	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Wilson and Smith 1983(143)	No	S	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Low

Key Question 1 Case-Control Study Quality Assessments

Reference	Items													Quality Category
	1	2	3	4	5	6	7	8	9	10	11	12	13	
McGwin et al. 2000(136)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate

Key Question 2 Cohort Study Quality Assessments

Reference	Items										Quality Category
	1	2	3	4	5	6	7	8	9	10	
Akinwuntan et al.(145)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Bouillon et al.(146)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Smith-Arena et al.(147)	S	S	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	Low
Soderstrom et al.(99)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Moderate
Lundberg et al.(148)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Moderate
Akinwuntan et al.(149)	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Moderate
Korner-Bitensky et al.(150)	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Moderate
Lundqvist et al.(142)	Yes	S	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Mazer et al.(151)	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Moderate
Nouri and Lincoln(152)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	Moderate
Nouri and Lincoln(153)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Nouri et al.(154)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate

Key Question 3 Case-Control Study Quality Assessments

Reference	Items													Quality Category
	1	2	3	4	5	6	7	8	9	10	11	12	13	
Harmsen et al., 2006(161)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	NR	Yes	Yes	Yes	Low
Hajat et al., 2004(162)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	NR	Yes	Yes	Yes	Low
Rodgers et al., 2004(163)	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	NR	Yes	Yes	Yes	Low
de Champvallins et al., 2001(164)	Yes	Yes	Yes	Yes	No	No	No	No	Yes	NR	Yes	NR	Yes	Low
Kaarisalo et al., 2000(165)	Yes	Yes	Yes	Yes	No	No	No	No	Yes	NR	Yes	Yes	Yes	Low
Zodpey et al., 2000(166)	Yes	NR	No	Yes	Yes	Yes	No	No	Yes	NR	Yes	NR	Yes	Low
Whisnant et al., 1996(167)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NR	Yes	Yes	Yes	Moderate

Key Question 3 Cohort Study Quality Assessments

Reference	Items										Quality Category
	1	2	3	4	5	6	7	8	9	10	
Howard et al., 1994(168)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate
Dennis et al., 1990(169)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Whisnant and Wiebers, 1987(170)*	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NR	Yes	Moderate
Ostfeld et al., 1973(172)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Moderate
Whisnant et al., 1973(173)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NR	Yes	Moderate

* Re-analyzes data from Whisnant et al., 1973(173) using population of Rochester, Minnesota from 1960-1964.

Key Question 3 Case-Control Study Quality Assessments

Reference	Items													Quality Category
	1	2	3	4	5	6	7	8	9	10	11	12	13	
Harmsen et al., 2006(161)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	NR	Yes	Yes	Yes	Low
Hajat et al., 2004(162)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	NR	Yes	Yes	Yes	Low
Rodgers et al., 2004(163)	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	NR	Yes	Yes	Yes	Low
de Champvallins et al., 2001(164)	Yes	Yes	Yes	Yes	No	No	No	No	Yes	NR	Yes	NR	Yes	Low
Kaarisalo et al., 2000(165)	Yes	Yes	Yes	Yes	No	No	No	No	Yes	NR	Yes	Yes	Yes	Low
Zodpey et al., 2000(166)	Yes	NR	No	Yes	Yes	Yes	No	No	Yes	NR	Yes	NR	Yes	Low
Whisnant et al., 1996(167)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NR	Yes	Yes	Yes	Moderate
Herman et al., 1983(171)	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	NR	Yes	Yes	Yes	Low

Appendix H: Sensitivity Analyses

Sensitivity Analyses (Key Question 3)

TIA and Risk Ratio

One Year Follow-up

Figure H-1. Removal of One Study at a Time

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Howard 1994	16.082	11.032	23.445	14.444	0.000
Dennis 1990	9.944	2.762	35.803	3.514	0.000
Whisnant 1987	6.984	2.250	21.679	3.363	0.001
	12.018	**5.657**	**25.529**	**6.468**	**0.000**

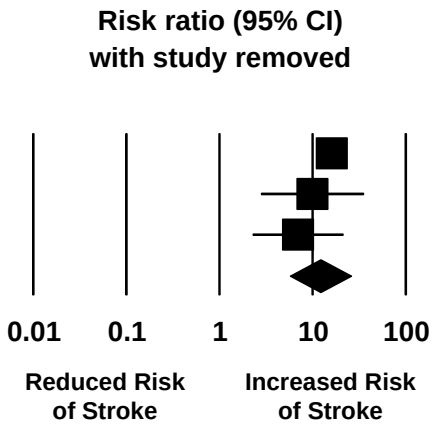


Figure H-2. Cumulative REMA (Highest Weight Study First)

Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Whisnant 1987	16.250	11.033	23.934	14.113	0.000
Howard 1994	9.944	2.762	35.803	3.514	0.000
Dennis 1990	12.018	5.657	25.529	6.468	0.000
	12.018	**5.657**	**25.529**	**6.468**	**0.000**

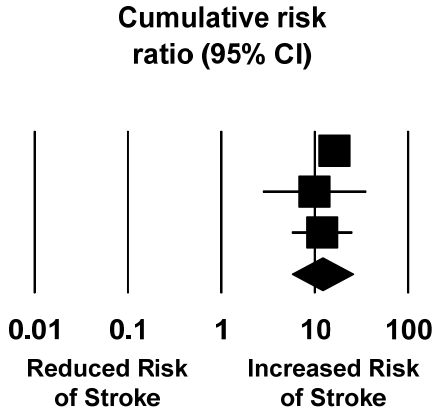


Figure H-3. Cumulative REMA (Most Recent Study First)

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Howard 1994	4.167	0.968	17.932	1.917	0.055
Dennis 1990	6.984	2.250	21.679	3.363	0.001
Whisnant 1987	12.018	5.657	25.529	6.468	0.000
	12.018	**5.657**	**25.529**	**6.468**	**0.000**

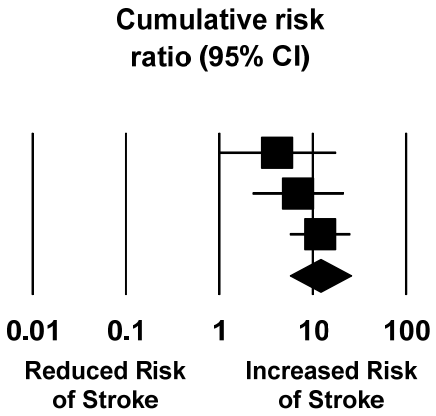
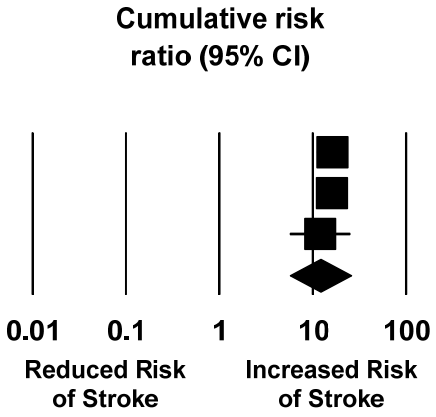


Figure H-4. Cumulative REMA (Oldest Study First)

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Whisnant 1987	16.250	11.033	23.934	14.113	0.000
Dennis 1990	16.082	11.032	23.445	14.444	0.000
Howard 1994	12.018	5.657	25.529	6.468	0.000
	12.018	**5.657**	**25.529**	**6.468**	**0.000**



Three Year Follow-up

Figure H-5. Removal of One Study at a Time

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Howard 1994	5.082	1.227	21.050	2.242	0.025
Whisnant 1987	2.692	1.771	4.091	4.635	0.000
Ostfeld 1973	7.645	3.348	17.456	4.828	0.000
	4.852	**1.599**	**14.717**	**2.789**	**0.005**

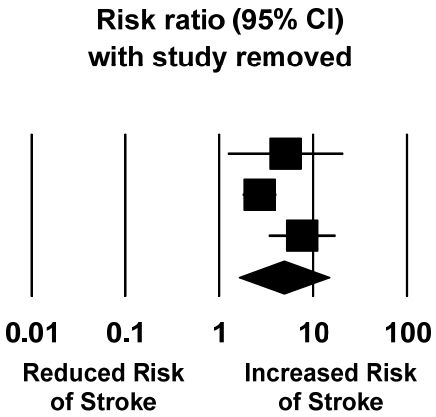


Figure H-6. Cumulative REMA (Highest Weight Study First)

Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Whisnant 1987	10.417	8.057	13.467	17.881	0.000
Ostfeld 1973	5.082	1.227	21.050	2.242	0.025
Howard 1994	4.852	1.599	14.717	2.789	0.005
	4.852	**1.599**	**14.717**	**2.789**	**0.005**

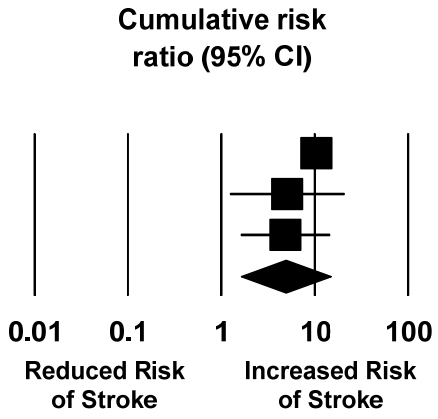


Figure H-7. Cumulative REMA (Most Recent Study First)

Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Howard 1994	4.308	1.615	11.488	2.918	0.004
Whisnant 1987	7.645	3.348	17.456	4.828	0.000
Ostfeld 1973	4.852	1.599	14.717	2.789	0.005
	4.852	**1.599**	**14.717**	**2.789**	**0.005**

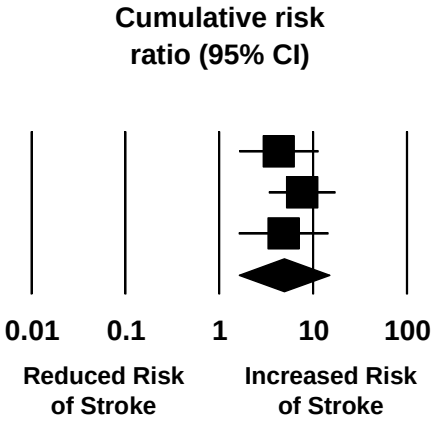


Figure H-8. Cumulative REMA (Oldest Study First)

Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Ostfeld 1973	2.443	1.661	3.593	4.536	0.000
Whisnant 1987	5.082	1.227	21.050	2.242	0.025
Howard 1994	4.852	1.599	14.717	2.789	0.005
	4.852	**1.599**	**14.717**	**2.789**	**0.005**

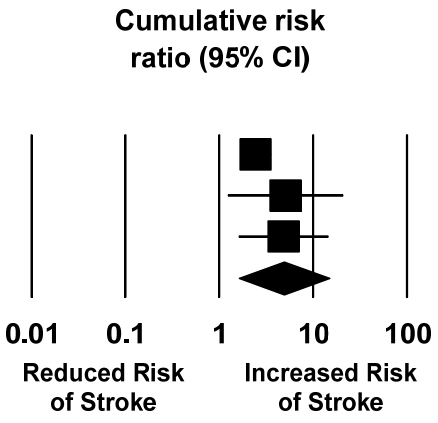


Figure H-9. Removal of One Study at a Time

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Hajat 2004	3.862	2.597	5.744	6.671	0.000
Rodgers 2004	5.764	3.164	10.499	5.725	0.000
Champvallins 2001	5.823	3.271	10.363	5.990	0.000
Kaarisalo 2000	4.924	2.735	8.867	5.313	0.000
Zodpey 2000	4.870	2.813	8.429	5.655	0.000
Whisnant 1996	4.919	2.664	9.082	5.091	0.000
Herman 1983	5.013	2.754	9.125	5.275	0.000
	4.978	2.965	8.360	6.069	0.000

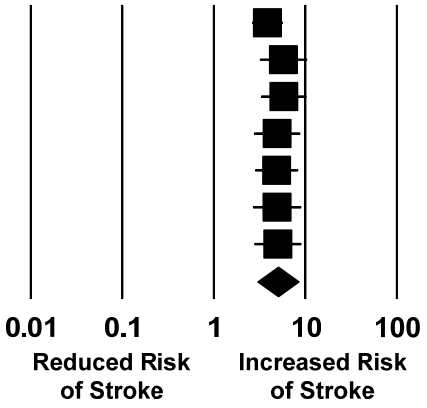


Figure H-10. Cumulative REMA (Highest Weight Study First)

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Rodgers 2004	2.460	1.726	3.506	4.981	0.000
Champvallins 2001	2.376	1.844	3.060	6.699	0.000
Whisnant 1996	3.129	1.838	5.324	4.204	0.000
Herman 1983	3.457	2.184	5.472	5.293	0.000
Kaarisalo 2000	3.735	2.464	5.660	6.210	0.000
Hajat 2004	4.870	2.813	8.429	5.655	0.000
Zodpey 2000	4.978	2.965	8.360	6.069	0.000
	4.978	2.965	8.360	6.069	0.000

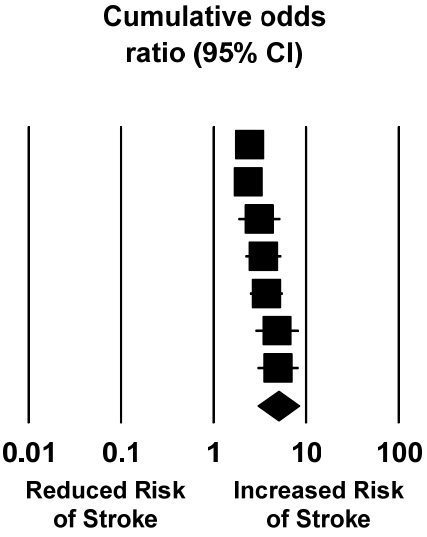


Figure H-11. Cumulative REMA (Most Recent Study First)

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Hajat 2004	20.500	10.008	41.991	8.256	0.000
Rodgers 2004	6.934	0.869	55.350	1.827	0.068
Champvallins 2001	4.594	1.682	12.551	2.974	0.003
Kaarisalo 2000	4.761	2.134	10.625	3.810	0.000
Zodpey 2000	4.955	2.382	10.308	4.281	0.000
Whisnant 1996	5.013	2.754	9.125	5.275	0.000
Herman 1983	4.978	2.965	8.360	6.069	0.000
	4.978	2.965	8.360	6.069	0.000

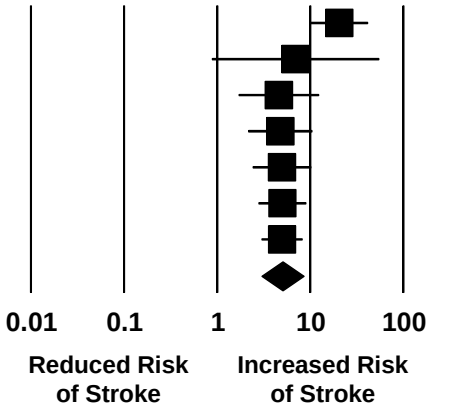
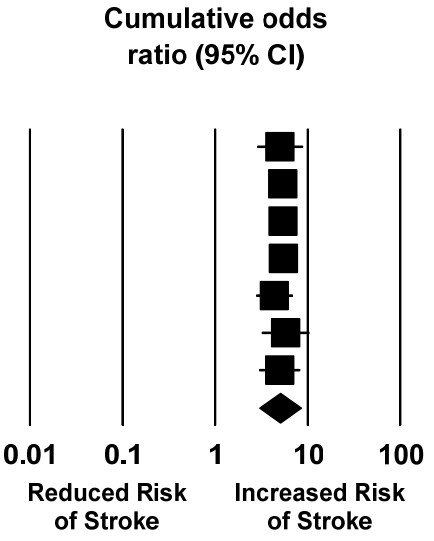


Figure H-12. Cumulative REMA (Oldest Study First)

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Herman 1983	5.016	2.816	8.932	5.477	0.000
Whisnant 1996	5.392	3.846	7.561	9.770	0.000
Kaarisalo 2000	5.420	4.025	7.299	11.129	0.000
Zodpey 2000	5.465	4.085	7.312	11.434	0.000
Champvallins 2001	4.374	2.750	6.958	6.231	0.000
Hajat 2004	5.764	3.164	10.499	5.725	0.000
Rodgers 2004	4.978	2.965	8.360	6.069	0.000
	4.978	2.965	8.360	6.069	0.000



Appendix I: Stroke Scales

NIH Stroke Scale

The NINDS tPA Stroke Trial No. ___ ___ - ___ ___ ___ - ___ ___ ___

Pt. Date of Birth ___ ___ / ___ ___ / ___ ___

Hospital _____ (___ ___ - ___ ___)

Date of Exam ___ ___ / ___ ___ / ___ ___

Interval: 1 □ Baseline 2 □ 2 hours post treatment 3 □ 24 hours post onset of symptoms 6 minutes 4 □ 7–10 days 5 □ 3 months 6 □ Other _____ (___ _____)

Time: ___ ___:___ ___ 1 □ am 2 □ pm

Directions: Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

IF ANY ITEM IS LEFT UNTESTED, A DETAILED EXPLANATION MUST BE CLEARLY WRITTEN ON THE FORM. ALL UNTESTED ITEMS WILL BE REVIEWED BY THE MEDICAL MONITOR, AND DISCUSSED WITH THE EXAMINER BY TELEPHONE.

Instructions

1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.

Scale Definition

0 = Alert; keenly responsive.

1 = Not alert, but arousable by minor stimulation to obey, answer, or respond.

2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).

3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, are flexic.

Score

_____

1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct — there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.

0 = Answers both questions correctly.

1 = Answers one question correctly.

2 = Answers neither question correctly.

_____

1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one-step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.

0 = Performs both tasks correctly

1 = Performs one task correctly

2 = Performs neither task correctly

_____

Instructions

2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.

Scale Definition

0 = Normal

1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present.

2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.

Score

_____

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to answer question 11.

0 = No visual loss

1 = Partial hemianopia

2 = Complete hemianopia

3 = Bilateral hemianopia (blind including cortical blindness)

_____

4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.

0 = Normal symmetrical movement

1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling)

2 = Partial paralysis (total or near total paralysis of lower face)

3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)

_____

Instructions

5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "9" and the examiner must clearly write the explanation for scoring as a "9."

Scale Definition

0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds.

1 = Drift, Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.

2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.

3 = No effort against gravity, limb falls.

4 = No movement

9 = Amputation, joint fusion, explain:

_____

5a. Left Arm

5b. Right Arm

0 = No drift, leg holds 30 degrees position for full 5 seconds.

1 = Drift, leg falls by the end of the 5-second period but does not hit bed.

2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity.

3 = No effort against gravity, leg falls to bed immediately.

4 = No movement

9 = Amputation, joint fusion explain:

_____

6a. Left Leg

6b. Right Leg

8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands),

legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0.

The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.

0 = Normal; no sensory loss.

1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched.

2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.

Instructions

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9," and the examiner must clearly write the explanation for not scoring. In case of blindness, test by touching nose from extended arm position.

Scale Definition

0 = Absent

1 = Present in one limb

2 = Present in two limbs

If present, is ataxia in

Right arm 1 = Yes 2 = No

9 = amputation or joint fusion, explain

_____

Left arm 1 = Yes 2 = No

9 = amputation or joint fusion, explain

_____

Right leg 1 = Yes 2 = No

9 = amputation or joint fusion, explain

_____

Left leg 1 = Yes 2 = No

9 = amputation or joint fusion, explain

_____

Score

_____

_____

_____

_____

_____

9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one-step commands.

0 = No aphasia, normal

1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card from patient's response.

2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.

3 = Mute, global aphasia; no usable speech or auditory comprehension.

_____

Instructions

10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech may the item be scored "9," and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.

Scale Definition

0 = Normal

1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty.

2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.

9 = Intubated or other physical barrier, explain

_____

Score

_____

11. Extinction and Inattention (formerly Neglect):

Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.

0 = No abnormality.

1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.

2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.

_____

A. Distal Motor Function: The patient's hand is held up at the forearm by the examiner and patient is asked to extend his/her fingers as much as possible. If the patient can't or doesn't extend the fingers, the examiner places the fingers in full extension and observes for any flexion movement for 5 seconds. Only the patient's first attempts are graded.

Repetition of the instructions or of the testing is prohibited.

0 = Normal (No flexion after 5 seconds)

1 = At least some extension after 5 seconds, but not fully extended. Any movement of the fingers which is not upon command is not scored.

2 = No voluntary extension after 5 seconds. Movements of the fingers at another time are not scored.

a. Left Arm

b. Right Arm

_____

_____

Barthel Index

Full credit is not given for an activity if the patient needs even minimal help/supervision. A score of 0 is given when patient cannot meet criteria as defined.

1. Feeding

10 □ Independent; feeds self from tray or table; can put on assistive device if needed; accomplishes feeding in reasonable time.

5 □ Assistance necessary with cutting food, etc.

0 □ Cannot meet criteria

2. Moving (from wheelchair to bed and return)

15 □ Independent in all phases of this activity.

10 □ Minimal help needed or patient needs to be reminded or supervised for safety of 1 or more parts of this activity.

5 □ Patient can come to sitting position without help of second person but needs to be lifted out of bed and assisted with transfers.

0 □ Cannot meet criteria

3. Personal Toilet

5 □ Can wash hands, face; combs hair, cleans teeth. Can shave (males) or apply makeup (females) without assistance; females need not braid or style hair.

0 □ Cannot meet criteria

4. Getting On and Off Toilet

10 □ Able to get on and off toilet, fastens/unfastens clothes, can use toilet paper without assistance. May use wall bar or other support if needed; if bedpan necessary patient can place it on chair, empty, and clean it.

5 □ Needs help because of imbalance or other problems with clothes or toilet paper.

0 □ Cannot meet criteria.

5. Bathing Self

5 □ May use bath tub, shower or sponge bath. Patient must be able to perform all functions without another person being present.

0 □ Cannot meet criteria.

6. Walking on Level Surface

15 □ Patient can walk at least 50 yards without assistance or supervision; may use braces, prostheses, crutches, canes, or walkerette but not a rolling walker. Must be able to lock/unlock braces, assume standing or seated position, get mechanical aids into position for use and dispose of them when seated (putting on and off braces should be scored under dressing).

10 □ Assistance needed to perform above activities, but can walk 50 yards with little help.

0 □ Cannot meet criteria.

7. Propelling a Wheelchair

Do not score this item if patient gets score for walking.

5 □ Patient cannot ambulate but can propel wheelchair independently; can go around corners, turn

around, maneuver chair to table, bed, toilet, etc. Must be able to push chair 50 yards.

0 □ Cannot meet criteria.

8. Ascending and Descending Stairs

10 □ Able to go up and down flight of stairs safely without supervision using canes, handrails, or crutches

when needed and can carry these items as ascending/descending.

5 □ Needs help with or supervision of any of the above items.

0 □ Cannot meet criteria

9. Dressing/Undressing

10 □ Able to put on, fasten and remove all clothing; ties shoelaces unless necessary adaptations used. Activity includes fastening braces and corsets when prescribed; suspenders, loafer shoes and dresses opening in the front may be used when necessary.

5 □ Needs help putting on, fastening, or removing clothing; must accomplish at least half of task alone within reasonable time; women need not be scored on use of brassiere or girdle unless prescribed.

0 □ Cannot meet criteria.

10. Continence of Bowels

10 □ Able to control bowels and have no accidents. Can use a suppository or take an enema when necessary (as for spinal cord injury patients who have had bowel training).

5 □ Needs help in using a suppository or taking an enema or has occasional accidents.

0 □ Cannot meet criteria.

11. Controlling Bladder

10 □ Able to control bladder day and night. Spinal injury patients must be able to put on external devices and leg bags independently, clean and empty bag, and must stay dry day and night.

5 □ Occasional accidents occur, cannot wait for bed pan, does not get to toilet in time or needs help with external device.

0 □ Cannot meet criteria.

Modified Rankin Scale

0 □ No symptoms at all.

1 □ No significant disability despite symptoms; able to carry out all usual duties and activities.

2 □ Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.

3 □ Moderate disability requiring some help, but able to walk without assistance.

4 □ Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.

5 □ Severe disability; bedridden, incontinent, and requiring constant nursing care and attention.

Glasgow Outcome Scale (GOS)

1 □ Good recovery — patient can lead a full and independent life with or without minimal neurological deficit.

2 □ Moderately disabled; patient has neurological or intellectual impairment but is independent.

3 □ Severely disabled. Patient conscious but totally dependent on others to get through daily activities.

4 □ Vegetative survival.

5 □ Dead.

Hunt and Hess Classification of Subarachnoid Hemorrhage Classification Symptoms

Grade I Asymptomatic of minimal headache and slight nuchal rigidity.

Grade II Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy.

Grade III Drowsiness, confusion, or mild focal deficit.

Grade IV Stupor, moderate to severe hemiparesis, possible early decerebrate rigidity and vegetative disturbance.

Grade V Deep coma, decerebrate rigidity, moribund appearance.

The University of Cincinnati Patient Care Services Dysphagia Screen

• Please elevate patient to at least a 45–50 degree angle prior to dysphagia screen to allow the patient to achieve the best screen possible.

• Please circle the appropriate item.

Present Feeding Status: NG NI PEG NPO

Patient receiving tube feedings prior to dysphagia screen? yes no

Current Tube Feeding: _____

Date started: _____ Time started: _____

Hx. of Aspiration: No Yes Unknown

Controls Secretions: Normal Drools/Coughs Requires suctioning

Consciousness: Alert Lethargic Obtunded

Voice Quality: Normal Impaired Wet/gurgle *

Follows Commands: Consistent Impaired Impaired/poor attention *

Spontaneous Cough: Strong Weak Absent

Facial Weakness: Normal Flattened Unilateral weakness nasolabial fold (air escapes from closed lips)

Facial Sensation: Normal V1, V2, V3 Unilateral facial analgesia sensory loss

Soft Palate Elevation: Symmetrical Asymmetrical No elevation, unable to test *

Tongue Strength: Moves tongue Tongue deviates to No movement * circumorally one side

Lip Closure: Normal Weak Not achieved

Swallow: Within 2 sec. Delayed No swallow *

Speech Therapy Consult: Not required Consult required

* Categories: Speech Therapy should be consulted for formal swallowing evaluation