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Medicine & Health
RHODE ISLAND

# Stroke

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## COMMENTARIES



## CONTRIBUTIONS

*Special Theme*: **STROKE**
*Guest Editor*: **Brian Silver, MD**



## COLUMNS



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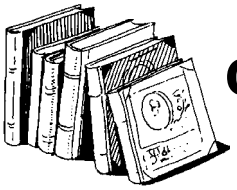

# Commentaries

## Reducing Risk Factors

**A FEW WEEKS BEFORE I WROTE THIS AN** article got a lot of press attention because it discussed seven "risk factors" for Alzheimer's disease, and stated, or at least inferred, that half of future cases could be avoided by reducing these risk factors. Thinking more and exercising more were the two that stick out in my mind, although smoking and weight loss were also on the list. This was in the newspapers, and the TV news.

Today I read a review article in Archives of Neurology, an esteemed publication with a high impact factor, reporting that there were no known modifiable risk factors for Alzheimer's disease. Being a half-empty kind of guy by nature, and, if I hadn't been born a skeptic certainly have had it pounded into me over the past few decades of clinical research, this review article made much more sense to me. It also brought to the fore the problems with the interpretation of risk factors.

The first issue is the misunderstanding many have of what the term risk factor means. We think of risk factors as properties that an individual has which increase the risk of that person having a certain outcome. We have learned that cigarette smoking is a risk factor for certain types of cancer. If people stop smoking they are less likely to develop various cancers. Cigarette smoke has chemicals that alter DNA and cause cancer. There is a causal relationship. Epidemiology pointed to potential causes, and at least one was found. Too often, as is the case with the Alzheimer work, one leaps from "associations" to "risk factors." To have a risk factor puts you at greater risk to develop the problem. This does not mean that there is actually any direct risk. For example, people who are heavy alcohol drinkers are at increased risk of lung cancer. In this case, the risk is directly attributable to the link between alcohol consumption and cigarettes. The risk of lung cancer is not increased in alcohol imbibers who do not smoke. If you live in the Azores you are far more likely to develop Machado-Joseph Disease, an inherited neurological disorder, than if you live in Kansas, because the illness has a nidus in the Azores. Simply living on one of the islands confers a "risk" but, of course, this is a nonsensical association.

I prefer the term "associations" to "risk" when the connection is only epidemiologic. I think that the term "risk" suggests to most readers a causal relationship. People who have AD were more likely to have been overweight, less well educated, less exercised, used their "thinking skills" less, and to have smoked more. This often suggests that overweight people who smoke and don't think are more likely to develop Alzheimer's disease, from which one deduces that losing weight, stopping smoking and solving physics problems will reduce the risk. The epidemiological studies do not, of course, suggest this. What they've found is that when one compares people with AD to those without and one analyzes data on their younger years, there were differences in behavior or weight, or blood pressure or something else. Too often these associations are interpreted as causal risk factors. Being overweight is associated with developing AD so you should lose weight. While this may be true, it is far more likely to be like suggesting smoke removal to stop a fire. It has been demonstrated that Parkinson's disease patients are less likely to have smoked than people who do not have PD. Does this mean that smoking cigarettes prevents PD, or might it mean that people who are fated to develop PD are less likely to want to smoke because of brain differences that are present many years before the disease is known to have taken hold?

There have been many epidemiological studies and, no matter what sophisticated statistical analyses used, the more questions you ask, the more likely you are to find "significant" correlations. Correlations are not risk factors. They are associations. And, although they clearly showed the connection between cigarettes and lung cancer, they mostly produce associations later found to be spurious. In current times they may lead to expensive clinical trials as clinical trialists run out of good ideas and the demand for solutions increases. Witness the many studies showing vitamin D deficiency associated with a multitude of disorders, few of which improve with vitamin D supplements.

The second problem I have, as a neurologist, is what it means to "think" and what the effect of thinking is on brain structure and function. With the exception of people with certain brain diseases, I believe that everyone thinks all the time, although, perhaps Zen masters may not, but there aren't enough of them to alter any statistical analyses. What many people believe constitutes the sort of thinking that reduces Alzheimer's disease is solving problems, translating Homeric Greek and listening to classical music. I like to listen to classical music and to solve problems, but I doubt this is "better" in the sense of protecting me against Alzheimer's disease, than thinking with the same intensity about dinner or my car or what movie I want to watch on Netflix.

I am unsure if anyone believes that spending time solving differential equations is more protective than studying Greek, or thinking about when to plant your bulbs for next year. If one posits the notion that learning increases synaptic connections, and that the more synaptic connections one has, the greater the brain power you've stored up for the decline that comes later when Alzheimer's starts to draw down the account, then the idea of thinking as a protective exercise makes sense. But is it at all plausible that such a simplistic hypothesis could be true? And if so, what would constitute the type of thinking that would accomplish this? Should we rig up instruments to detect how much energy our brains are using?

Perhaps it would be better to use *less* energy to protect the brain from oxidative byproducts of too much thinking? There's an old joke about the futuristic person who goes to the brain store to buy a new brain. He finds Mozart's brain available for a huge amount of money, and Einstein's for even more, so he asks the manager if there aren't even more expensive brains to consider buying. He's taken to the locked vault where he's shown a brain that costs 10 times as much as Einstein's. He's told that this brain belonged to (pick your own name to put here). It costs more than Einstein's because it's never been used.

Perhaps there are differences in types of thinking. Perhaps problem solving is a different type of thinking than trying to guess how the ballgame will end. Perhaps daydreaming is good and physics is bad, or vice versa. And is abstract thinking (algebraic geometry) better or worse than non-abstract thinking (differential equations)?

Does anyone believe that because higher levels of education are associated with a lower risk of developing AD that everyone should go to college and that the cost will be offset by the reduced rate of AD 60 years later?

The closer we look at diseases, the more complex and challenging they become. Epidemiological studies to determine true risk factors, provide questions, not answers.

**– Joseph H. Friedman, MD**

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# Where Are the Spirits of Yesteryear?

**What is the dynamic force behind civilization? Patrick** McGovern, a contemporary archeologist, declares that it is the quest for intoxication. Certainly a spirited response; and while it may sound hyperbolic in the eyes of the temperance movement, it is nonetheless a sadly accurate presumption.

The first mention of intoxicating fluids in the Bible occurs when post-diluvian Noah plants a vineyard at the base of Mount Ararat, consumes the wine and becomes drunken (Genesis 9:20-21.) And thus, according to Scripture, a man who had found singular grace in the eyes of the Lord is quickly besotted by a wine derived from the berries of his own vineyard. G. K. Chesterton (1874 – 1936), reflecting upon the abating floods, has then elaborated on the biblical tale:

> And Noah he often said to his wife
> when he sat down to dine,
> I don't care where the water goes
> if it doesn't get into the wine.

The origins of wine and other fermented intoxicants are lost in a swirl of legends, heroic myths and apocryphal fairy tales. One of the most vivid of these tales speaks of the mythical king of Persia, Jamshid, the fourth ruler of the great Pishdadian dynasty of greater Iran. The legend declares that Jamshid banished one of his harem wives who, in despondency, then sought a poison for suicide. In her search for a lethal substance she came upon an abandoned vat of old, fermented fruit juice; and thinking it a poison, she drank of it, thus discovering, instead, that the drink provided a form of unanticipated exultation. In haste she returned to King Jamshid, shared her inebriant discovery with him and was promptly returned to her harem status. And thus, one legend tells us, the discoverer of a principal form of addictive slavery was rewarded by hastening her return to another form of slavery.

Unromantic chemists, however, have provided science with a means of determining the age of recovered artifacts by a radioactive measuring process called carbon-dating; and secondly by infrared spectrophotometry they possess a procedure that can analyze small amounts of dried residue clinging to the interior of ancient pottery and thereby identify some substances found in wines and thus may infer that the vessel had once stored wine in the past; and further, they are then able to identify the regions from whence wine-making had originated.

And so, scientists tell us that the first evidence of wine consumption is found in the Neolithic settlements in the Caucasus foothills, some 9,000 years ago. It is likely that the berries were foraged from wild grape vine or other fruits. The development of terracotta pottery, during the late Neolithic age, allowed for the storage of excess wines and hence provided modern-day chemists with ancient specimens in the form of wine-stained shards which were amenable to modern analysis.

Gene-mapping of the numerous grape cultivars, currently employed in the extensive wineries of the Mediterranean and Asia Minor has verified that they are traceable to the wild grape species of that southern Caucasus area situated between the wine-dark waters of the Black and Caspian Seas.

Domestication of the grape vine was the next step in the evolution of viticulture; and there is evidence that this agricultural advancement simultaneously evolved in many Mediterranean and Middle East sites including Macedonia in northern Greece and in Mesopotamia. Physical evidence of viticultural specialization, a necessary phase in the evolution of the industry (with wine presses and facilities for the storage and shipment of the ultimate fermented product), is found throughout the southern Balkans, Mediterranean and many regions in the Middle East.

With the notable exception of Islam (the Prophet had declared that there is the devil in every grape), the many religions that took origin within this nursery of civilization readily incor-

porated wine as a ceremonial component of their rituals; and inevitably gods – such as Dionysus, god of revelry – were honored as progenitors of the wines used in their altar celebrations. And thus, mass intoxication is now defined as a bacchanalia, a dubious tribute to Bacchus, the Latin variant of Dionysus. Many orders of monks, such as the Carmelites and Benedictines, also labored to produce distinctive varietals. Indeed, Dom Perignon, a name identified closely with champagne, was a Benedictine monk.

Where ever vineyards can be planted – from the valleys of Tuscany, the foothills of California to the plains of Shiraz - man has discovered and savored the questionable gift of wine. Isak Dinesen (1885 – 1962) reflected upon this: "What is man, when you come to think upon him, but a minutely set, ingenious machine for turning, with infinite artfulness, the red wine of Shiraz into urine ?"

– Stanley M. Aronson, MD

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# Foreword: An Update in Advances for Stroke

***Brian Silver, MD***

**Much has occurred in the last decade with respect to stroke** in the areas of public education, prehospital care, acute treatment, rehabilitation, and secondary prevention. In the series of reviews that follow, individuals involved in the care of stroke patients from across the state cover the spectrum of care for stroke. The first article describes primary prevention strategies and public education resources; the second surveys the current state of emergency medical services in Rhode Island; the third emphasizes the importance of early treatment with thrombolytic therapy and efforts to improve time to treatment; the fourth reviews the science behind stroke units; the fifth examines the broad range of opportunities for stroke rehabilitation; and the sixth discusses the latest in secondary stroke prevention from hypertension treatment to new options in anticoagulation. We hope these reviews serve to stimulate discussion and continue to improve care for patients across Rhode Island.

*Brian Silver, MD, is Director at the Stroke Center at Rhode Island Hospital.*

**Disclosure of Financial Interests:**

Brian Silver, MD, has served as a consultant for Abbott Vascular and as a defense expert in medical malpractice cases of stroke.

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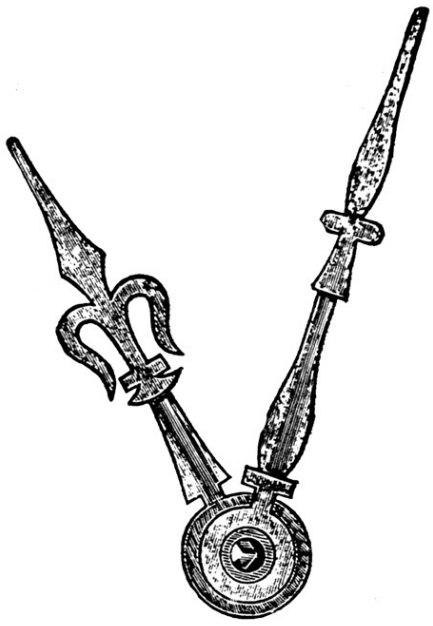

# Emergency Medical Services in Stroke Care: A Rhode Island Perspective

*John H. Potvin, EMT-C*

**Advances over the past decade in acute** stroke care, including the introduction of fibrinolytic and other short-term therapies, have highlighted the critical role of **emergency medical services** (**EMS**) agencies in optimizing stroke care.[1] Statistics show 29-65% of all stroke patients are treated by EMS.[2] In order to ensure the greatest outcomes for stroke patients, EMS must be considered an integral part of the stroke care system. The goal of prehospital care must be to deliver the greatest number of stroke patients to a primary stroke center within established timelines to provide for the best outcomes.

## Rhode Island EMS

In order to understand the role of EMS within the stroke system of care, we must first understand the EMS system in Rhode Island. The **Rhode Island Department of Health** (**RIDH**) Division of Emergency Medical Services in conjunction with the **Rhode Island Ambulance Service Coordinating Advisory Board** (**RIASCAB**) is responsible for the planning, licensing, development, and administration of a comprehensive statewide plan for emergency medical services for the State of Rhode Island. The RIASCAB is comprised of 23 members from various geographic regions of the State, and several areas of expertise.[3] In addition to the Department of Health staff, the State retains a physician medical consultant to oversee clinical aspects of the system including the Rhode Island Prehospital Care Protocols and Standing Orders. The most unique characteristic of Rhode Island emergency medical services is the absence of a mandate requiring individual agencies to have a medical director.

While the most visible component of the system is the nearly 400 licensed ambulances that are positioned in local communities, the State is comprised of 95 separate EMS agencies. The fire service makes up the majority of the EMS service in Rhode Island followed by third party municipal and commercial agencies. The volume and variety of agencies creates a complexity as we look at stroke care because each service has different resources, motivations, education, and experience.

In addition to the breakdown of agency type, we must also analyze the type of provider functioning within the agencies. Currently, there are 4200 licensed EMS personnel in the State, broken down into the following categories: **emergency medical technician** (**EMT**)-Basic, EMT-Cardiac, and EMT-Paramedic. Predominately, the prehospital provider is the EMT-Cardiac, which is a provider level unique to Rhode Island. There are also 91 licensed EMT- instructor/coordinators.

## Prehospital care stroke protocol

The current prehospital stroke care protocol was developed in December of 2002, prior to the recognition of the importance of EMS in stroke care. Ironically, it was not just hospitals that did not realize the importance of EMS; prehospital providers themselves did not realize that their care had such a profound affect on stroke patient outcomes. The Cincinnati Prehospital Stroke Scale is used as an assessment tool in addition to recognition criteria of monocular blindness, vertigo, or ataxia, without impaired consciousness.[6] In patients who are impaired, providers are referred to the Impaired Consciousness Protocol. Current treatment protocols include: determination of when the patient was last known without symptoms, withholding the administration of oral medications, and administration of oxygen at the highest concentration tolerated. The protocol directs the use of the prehospital stroke scale to determine the treatment priority yet there is no reference to transport the stroke patient to a primary stroke center.[4] The protocol is a good foundation but must be updated and reorganized to reflect current recommendations for prehospital stroke care and the provisions of the Stroke Prevention and Treatment Act of 2009.[9]

**Table 1. Guidelines for EMS Management of Patients with Suspected Stroke[2]**

| Recommended | Not Recommended |
|---|---|
| Manage ABCs | Dextrose-containing fluids in non-hypoglycemic patients |
| Cardiac monitoring<br>Intravenous access<br>Oxygen (as required 02 saturation <92%) | Hypotension / excessive blood pressure reduction<br>Excessive intravenous fluids |
| Assess for hypoglycemia | |
| NPO | |
| Alert receiving facility | |
| Rapid transport to the closest appropriate facility capable of treating acute stroke | |

## American Stroke Association Recommendations

The effective integration of EMS for stroke involves complex interactions among the public, 9-1-1 call center personnel, EMS providers, emergency department providers, and stroke care specialists. The most important goals for prehospital care for stroke patients include the identification of the stroke patient in the field, the provision of appropriate prehospital care to the patient, and the transport of the patient to the most appropriate hospital. All of these goals should be achieved in the shortest amount of time possible.[1]

From an EMS system perspective, the **American Stroke Association (ASA)** 2004 Stroke Systems Task Force's original recommendations for EMS in the context of stroke care fall within the following four categories:[1]

- Activating and dispatching the EMS response for stroke patients. Stroke systems should require appropriate processes that ensure rapid access to EMS for acute stroke patients.
- EMS responders should use protocols, tools, and training that meet current ASA/AHA guidelines for stroke care.
- Prehospital providers, emergency physicians, and stroke experts should collaborate in the development of EMS training, assessment, treatment, and transportation protocols for stroke.
- Patients should be transported to the nearest stroke center for evaluation and care if a stroke center is located within a reasonable transport distance and transport time. The determination needs to take into account issues such as the availability of stroke centers and geography and whether transportation to a stroke center is possible within the appropriate time for acute therapeutic interventions.

Recent clinical guidelines for EMS personnel are established in Stroke: Guidelines for the Early Management of Adults with Ischemic Stroke, which was published in 2007, five years after the current Rhode Island Prehospital Care Protocols and Standing Orders for stroke were written. Guidelines for EMS management of stroke patients are presented in Table 1.

## Revised prehospital care stroke protocol

The Rhode Island Stroke Task Force, in collaboration with the Rhode Island Stroke Coordinators Network, and the American Stroke Association, has drafted an updated prehospital stroke protocol has been approved by the Rhode Island Department of Health and the RIAS-CAB. The revised protocol is based on the recommendations set forth in Stroke: Guidelines for the Early Management of Adults with Ischemic Stroke as well as the expertise of local stroke experts.

The revised protocol places emphasis on the use of the **Face Arm Speech Time (FAST)** test based on evidence that prehospital providers achieved high levels of detection and diagnostic accuracy for stroke using FAST.[5] The original recognition criteria were left in place as it was felt that abrupt disturbance of gait and vision disturbances may be the only signs and symptoms in a small number of stroke patients. In addition to wording that reflects not administering aspirin or other medications, the patient should be kept NPO.

Following initial assessment there has been a prioritization of determining the last known well time. In addition to determining the time of onset, the protocol also suggests transporting a witness with the patient or obtaining contact information such as a cell phone number which can be provided to the hospital staff. There is also specific guidance as to important aspects of patient history which should be obtained and documented.

Treatment focuses on obtaining blood glucose analysis to rule out hypoglycemia. Administration of high-flow oxygen has been changed to the use of supplemental oxygen to maintain normal pulse oximitry based on recognized clinical guidance.[10] For **advanced life support providers (ALS)**, the initiation of intravenous access utilizing normal saline solution and the acquisition of an EKG should occur during transport.

The most important component of the revised protocol is designating a **primary stroke center (PSC)** as the preferred receiving facility for suspected stroke patients. This revision reflects the recommendation as set forth by the ASA and the Rhode Island Stroke Prevention and Treatment Act of 2009. The protocol directs providers to contact medical control at the closest PSC. If a PSC is within a 30-minute transport time, it should be the preferred receiving hospital for patients with suspected stroke.

## Areas of improvement for Rhode Island

Although stroke patients receive quality care in Rhode Island, there is room for improvement as we move forward in a coordinated effort to improve outcomes for the stroke patients of our State. The areas that need improvement to meet established ASA recommendations are: (1) educational standard, (2) feedback, (3) **continuous quality improvement (CQI)** and (4) qualified medical dispatch.

RIDH licenses EMTs to three levels: Basic, Cardiac, and Paramedic. These levels of licensure vary in length from 130 to 1200 hours. Based on the duration of the whole training course, minimal time is dedicated specifically to stroke care in an initial prehospital provider course. RIDH requires recertification every three years with scant attention specifically geared toward stroke education. The ASA recommends that 100% of EMS providers complete a minimum of two hours of instruction on stroke assessment and care as part of their required continuing medical education for certification and re-licensure.[1]

Potential roadblocks to increasing the educational component are time, money, and resources. As prehospital providers struggle to meet the demands of the rapidly changing healthcare system, stroke is just one of the many areas that require attention. As previously stated, the majority of the prehospital providers in the State are employed by municipalities. Due to the economic climate, funding that may have been used to provide stroke education is being reallocated. In addition, as RIDH looks toward acceptance of the **Department of Transportation's (DOT)** National Standard Curriculum for all Emergency Medical Service Personnel, there is limited stroke-related subject matter despite the importance of identifying stroke patients.[7]

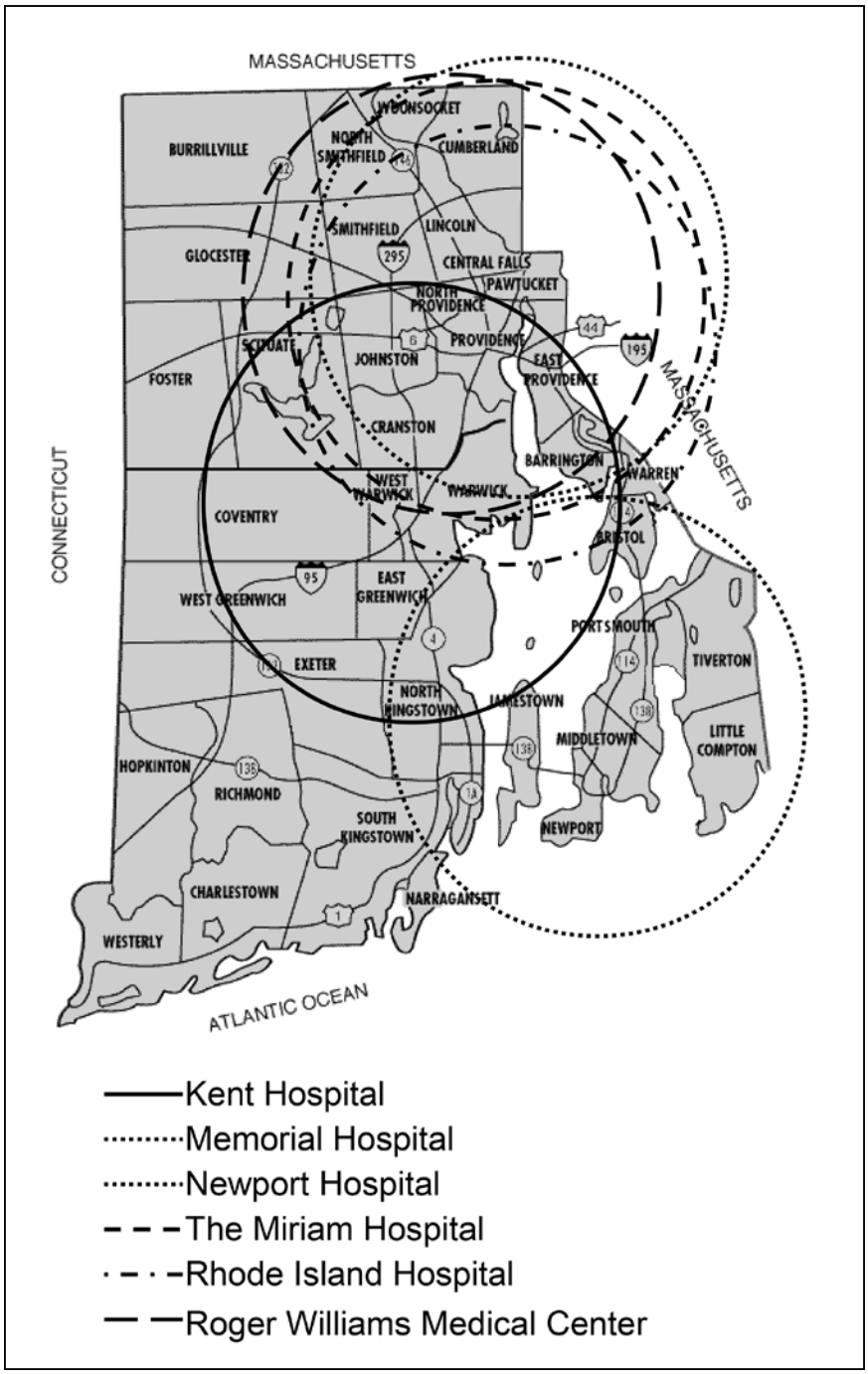


Figure 1. A geographical representation of 30 minute transport times to Rhode Island stroke centers

Many opportunities exist to integrate EMS into the stroke system. (1) Stroke experts can make presentations to EMS agencies. (2) EMS agencies can host stroke experts for ride-alongs. (3) Stroke centers can make contact information available to answer EMS/stroke related questions. (4) Quick-reference stroke educational materials can be made available to EMS personnel. (5) Networking opportunities between EMS and stroke center personnel should be embraced.

The ASA emphasized the importance of feedback when it issued the recommendation that feedback be provided to EMS on 100% of stroke patients.[1] Feedback is critical to improve stroke recognition by prehospital providers. It must be automatic and consistent to ensure that EMS understands when a stroke has been correctly identified in the field as well as capture those strokes that may have been missed. Feedback also allows providers to track patients through the continuum of care. The objective of feedback is improved care and coordination of stroke patients. Currently, Rhode Island lacks a system of feedback from the hospital to EMS agencies.

The greatest obstacle of feedback to EMS is the **Health Insurance Portability and Accountability Act** (**HIPAA**). In an effort to maintain confidentiality of patient's protected medical information, feedback regarding patient outcome becomes a neglected process. In addition to the obstacles that must be overcome for the sake of confidentiality, feedback requires time and personnel that many facilities may not have to devote to the process.

HIPAA permits providers to use and disclose protected health information for certain healthcare operations; many CQI activities fall squarely within the healthcare operation exception.[8] Stroke experts and EMS leaders must work together to develop a system of feedback that is timely, meaningful, and most of all achievable. Rhode Island should research and build upon the methods of feedback used in successful stroke systems in other states. One example is the feedback tool used by the Saint Luke's Brain and Stroke Institute in Kansas City, Missouri. Debbie Summers, Advanced Practice Registered Nurse and Stroke Program Coordinator at Saint Luke's explained to me, during a personal communication, that Saint Luke's provides feedback on 100% of stroke patients transported by EMS who receive intervention at the stroke center. The feedback provides pre- and post-treatment imaging, clinical outcome, and discharge disposition. The feedback tool can also provide contact information for local stroke experts and a brief explanation of treatment options.

The ASA also recognizes the critical need for CQI within the stroke system of care which should include assessments of all participants of the stroke care team including EMS. CQI must involve the exchange of information between hospitals and external agencies such as emergency medical service systems and dispatch centers. As an objective review of all aspects of care, the goal of CQI is to continuously improve care to stroke patients. In order for CQI to be effective, it must ensure that 100% of stroke patients are included in CQI activities.[1]

Recognizing the need to continuously improve care to all patients, RIDH

has mandated that all EMS agencies participate in CQI activities. RIDH is also in the process of developing a standardized **electronic patient care reporting** (**E-PCR**) system that is **National Emergency Medical Service Information System** (**NEMSIS**) compliant. The ability to electronically capture and compile NEMSIS data points will allow agencies to determine areas of proficiency and also areas where improvement is needed. Data can also be integrated into national databases for comparison.

The final area where Rhode Island must focus attention to improve outcomes for stroke patients is ensuring that EMS dispatchers are trained according to nationally recognized emergency medical dispatch guidelines. Currently, Rhode Island does not have a standard for personnel that dispatch EMS vehicles. RIDH has established a task force to make recommendations regarding a future standard. The ASA has recommended that 100% of call centers use dispatch guidelines that prioritize patients experiencing stroke symptoms as requiring a high-priority and receive the greatest level of care. EMS dispatchers should also be trained to correctly identify a high percentage of callers experiencing stroke and dispatch resources appropriately. In addition the ASA has established the guideline that the time period between the receipt of a call and the dispatch of EMS personnel should be less than 90 seconds for 90% of stroke related incidents.[1]

Mandating that all 911 dispatch centers use nationally recognized emergency medical dispatch guidelines reflecting the recommendations of the American Stroke Association for the care of stroke patients would ensure compliance with many of the recommendations. The greatest barriers to providing qualified medical dispatch are funding and resources. Until funding can be made available to staff dispatch centers to appropriate levels it will be difficult to accomplish the goal of training dispatchers to meet nationally recognized emergency medical dispatch guidelines

Effective August 1, 2011, the revised prehospital protocol recommends that a primary stroke center should be the preferred destination for stroke patients if they fall within a 30-minute transport radius of the facility. As shown in figure 1, not all Rhode Islanders have equal access to a primary stroke center; the western border of Rhode Island, especially toward the north and south portions of the state, lies beyond the limits of the revised protocol. The certification of additional hospitals as primary stroke centers will allow greater access for these areas that are beyond a 30-minute transport time.

## Conclusion

Recent data indicates that 29% to 65% of patients with signs or symptoms of acute stroke access their initial medical care via local EMS, which confirms the role of EMS in the chain of survival.[2] Based on these statistics, the Rhode Island system for stroke care must collaborate to ensure that prehospital providers are attaining the goals set forth by the American Stroke Association to improve the outcomes for stroke patients.

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# Intra-arterial Therapy for Acute Stroke: Trials and Tribulations

*Mahesh V. Jayaraman, MD, Richard A. Haas, MD, and Sun H. Ahn, MD*

**Stroke is a devastating disease,** affecting over 750,000 individuals in the United States each year. For patients with acute ischemic stroke, intra-venous **tissue plasminogen activator** (**tPA**) is a breakthrough treatment which improves outcomes when given within 4.5 hours from symptom onset.[1-6] However, some patients are ineligible for **intra-venous tPA** (**IVT**) and some fail to respond. In those instances, direct **intra-arterial therapy** (**IAT**) offers patients a treatment option. In this article, we will examine the past, present and future of IAT for acute ischemic stroke.

## Historical Background – Thrombolysis and thrombectomy

Soon after the publication of the NINDS trial in 1995, the earliest randomized trials of IAT for stroke were published.[7-8] The first such study, PROACT, used an intra-arterial infusion of **pro-urokinase** (**pro-UK**) for patients who were within six hours of symptom onset with acute MCA occlusion. The authors showed recanalization in 58% of patients receiving pro-UK as compared with only 14% of those receiving placebo.[7] However, the improvements in outcome were not as dramatic, with 31% of pro-UK patients having a **modified Rankin score** (**mRs**) of zero or one at 90 days compared with 21% in the placebo arm. Nevertheless, this study proved the safety and potential efficacy of this treatment paradigm and a larger, follow-up study, PROACT-II showed similar improvements in recanalization (66% pro-UK vs 18% placebo) and in clinical outcome (40% pro-UK patients had mRs zero to two at 90 days versus 25% of placebo). The most significant complications seen were symptomatic intracranial hemorrhage, which was seen in 10% of the pro-UK group in PROACT-II (as compared with 6% in the NINDS IV tPA study). Regardless, the improvements in outcome spurred a new era in acute stroke therapy.

The major limitations to intra-arterial thrombolytic infusion were related to the variability of clinical response. Recanalization could not be consistently achieved in a high percentage of patients, and even those patients who recanalized did not always improve. The thought of mechanically removing the embolus rather than relying on pharmacological thrombolysis has spurred the invention of the next generation of IAT devices (Figure 1). The first FDA approved device for this indication was the Merci retriever (Concentric Medical, Aliso Viejo, CA). The MERCI and Multi MERCI trials selected patients who were ineligible for IV tPA or who failed to clinically improve following IV tPA and were treated with mechanical thrombectomy with adjunctive thrombolysis. While recanalization rates were 70%, favorable clinical outcome (mRs zero to two) still remained low at 36%, and symptomatic hemorrhage rates were 9.8%[9]. Another new device, the Penumbra system (Penumbra Inc., Alameda, CA) showed recanalization rates of 82% with 25% of patients mRs zero to two at 90 days.[10] Both of these trials showed that despite increases in recanalization rates, the overall clinical outcomes have not improved substantially over IA tPA infusion. Patient selection, including the inclusion of patients with more proximal occlusion, as well as treatment up to eight hours from symptom onset may account for some of these differences in outcome.[11] However, when compared with patients in whom mechanical thrombectomy was attempted and unsuccessful, those in whom recanalization was obtained had significantly better clinical outcomes.[12] Certainly the availability of mechanical thrombectomy as a treatment option has further expanded our armamentarium. Unlike intra-arterial thrombolysis however, there have been no randomized trials comparing mechanical thrombectomy with no therapy or placebo infusion.

## Current directions – bridging and rescue therapy

Initially, patients with acute ischemic stroke were treated either with IV tPA or IAT, based on time from onset to presentation. However, with the expansion of the IVT window to 4.5 hours,[6] an alternative approach has gained traction – that of a combined paradigm where both intra-venous and intra-arterial techniques are combined with the goal of optimizing patient outcomes. In order to understand the rationale for this approach, we need to better define the subgroup of patients in whom IVT alone is unlikely to result in a good outcome. A re-analysis of the NINDS IV tPA trial stratified patients by admission **National Institutes of Health Stroke scale** (**NIHSS**), and showed the greatest benefit for IV tPA was for those patients with moderate strokes.[5] Indeed,

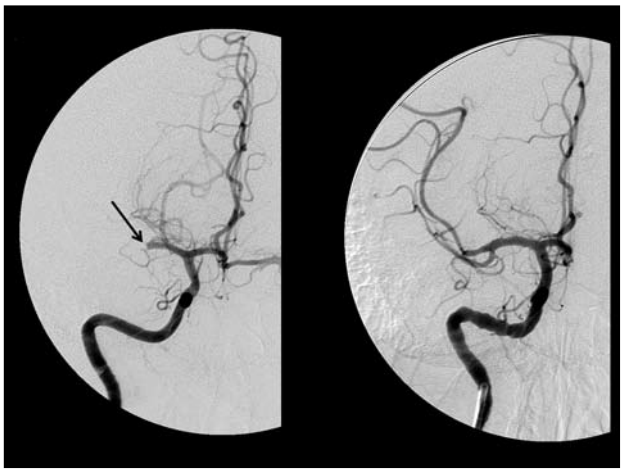

Figure 1. A frontal projection from a right internal carotid arteriogram demonstrates an abrupt occlusion of the proximal middle cerebral artery (arrows, left). This patient was ineligible for intravenous tPA due to recent abdominal surgery and was treated with intra-arterial mechanical thrombectomy. Post-treatment angiogram (right) shows complete restoration of flow. The patient had no residual deficit.

patients with an NIHSS of zero to five tended to have good outcomes regardless of therapy performed, those with NIHSS between six and 15 seemed to have the greatest benefit from IVT. Patients with more severe strokes (NIHSS 16 and above) did benefit from IVT, but the absolute benefit was not as great as with less severe strokes. Since the severity of the NIHSS is linked with the volume of infarction, it would follow that the more severe NIHSS is associated with a more proximal arterial occlusion.[13-14] It has been shown from trials using continuous **transcranial Doppler (TCD)** monitoring that the more proximal the arterial occlusion, the less likely that IV tPA will result in complete recanalization.[15] For example, only 6.3% of terminal **internal carotid artery (ICA)** occlusions recanalized with IV tPA as compared with 48% of more distal occlusion at the M2 branches of the MCA. A final determinant is the time to recanalization with IV tPA. Using TCD, Ribo showed that the vast majority of recanalization occurs in the first hour after the tPA bolus.[16] Based on these analyses, we would presume that patients with more severe strokes who fail to improve clinically within one hour from IV tPA administration may be those most likely to benefit from IAT. Patients with minor strokes (NIHSS one to five) are unlikely to benefit from IAT but should still receive IVT if eligible.

The safety of this combined approach has been demonstrated in the **interventional management of stroke (IMS)** trials.[17-18] The IMS-I trial showed safety, with a 6.4% symptomatic hemorrhage rate in patients treated with a lower dose of IV tPA combined with IA tPA infusion. In IMS-II, the recanalization rate was 62% and the rate of favorable clinical outcome at 90 days was 46%.[18] Interestingly, this rate was not significantly superior to the IV tPA treated group from NINDS, which raises the question of whether every patient needs a combined approach. The currently enrolling IMS-III trial randomizes patients into either IVT alone, or combined IVT plus IAT using either thrombolytic infusion or mechanical thrombectomy using Merci or Penumbra devices, and aims to show a difference in efficacy among the approaches.[19]

## Future goals – improving patient outcomes

Ultimately IAT for stroke needs to show improved patient outcomes. Despite gains in recanalization rates from the early days of PROACT, there is still a substantial cohort of patients who do not have a clinical benefit from IAT. One area of improvement is in device development. It would be logical to ask why the cardiac model of angioplasty and stenting for acute stroke is not routinely performed. Indeed, case series have demonstrated technical success when using stent based recanalization.[20] However, unlike cardiac lesions, an underlying stenosis is not usually present in intracranial occlusion. In addition, the tortuous anatomy can make delivery of stents challenging in the intracranial circulation. Nevertheless, there are newer devices which have shown promise in preliminary trials, and it is possible that self-expanding stents may play a role in IAT for stroke.[21-24] Another promising paradigm is the use of a combination stent and thrombectomy device, where the stent is used to open the vessel and after thrombolysis the device can be completely removed.[25-26] Future studies will need to show whether or not these technical developments can translate into improved clinical outcomes.

Improvements in patient selection and reductions in time to treatment may also improve outcomes. A strong linear relationship between time from symptom onset to recanalization and outcome has been shown for the IMS I and II trials,[27] with patients recanalized beyond seven hours from symptom onset not seeming to benefit from reperfusion. Stroke centers which perform IAT should have mechanisms in place to rapidly identify and treat appropriate patients. The use of advanced imaging studies such as **CT perfusion (CTP)**, or diffusion weighted MRI has been proposed as a means of better identifying patients who would benefit from IAT, but no series has shown a clear improvement in clinical outcomes when compared with using non-contrast CT alone.

## Summary

**Intra-arterial therapy (IAT)** for acute ischemic stroke has undergone great evolution during the past decade. While intra-venous therapy remains the standard of care for eligible patients, there are those patients in whom IV tPA is contra-indicated, or those who fail to improve following IV tPA. In those cases, patients with accessible arterial occlusions may benefit from IAT, especially when recanalization can occur within six hours from symptom onset. Future advancements in device development and patient selection may further improve outcomes.

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# Novel Stroke Rehabilitation Interventions

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**Stroke is a major cause of neurological** impairment; over half of stroke survivors have persistent upper limb impairment, and 25-50% of stroke survivors have persistent moderate to severe disability, especially in the realms of motor and language functions after completion of standard rehabilitation.[1] The prevalence of stroke survivors was over six million in 2006,[2] and is expected to increase as the population ages despite advances in stroke prophylaxis and acute treatment such as tPA. There is a pressing need to improve the neurologic function of stroke survivors.

The neurorehabilitation interventions employed by physical, occupational, and speech therapists on a practical level have changed little over the last 40 years. This is not for lack of trying. Determining efficacy of traditional and novel interventions has been hampered by methodological challenges including heterogeneous functional neuroanatomy and neuropathology, inadequate outcome measures (subjective, questionable ecological relevance), and logistical difficulties in studying a population with disabilities (impaired mobility and increased risk of medical problems to name only two which cause study subjects being easily lost to follow-up).

Fortunately, recent progress in neuroscience, particularly the discovery that the adult brain has surprising potential for plasticity especially after injury; and in the development of new technologies (computer science, biomechanics, cell and tissue manipulation, neuropharmacology) have driven the development of multiple promising interventions which could improve the function of those with neurological impairments.

Efforts are underway worldwide to determine how these techniques can be applied clinically. Critical questions include: which patients are most likely to benefit from interventions? Are there certain windows of opportunity during which an intervention would be most effective? Should different interventions be utilized in certain sequences?

Until recently the prospect of being able to answer these questions scientifically in a reasonable period of time was fantasy. However, new tools and novel techniques such as functional imaging and relevant surrogate outcome measures are helping to rapidly answer many of these questions and improve our understanding of neurological recovery.

We describe some of the most promising new restorative interventions for stroke rehabilitation currently being investigated. (Compensatory approaches, such as brain-computer interfaces, are beyond the scope of this paper.) Some, or all of them may, in some form, become standard components of neurorehabilitation programs in the coming years. Many of these techniques are being investigated for the rehabilitation of other neurologic conditions (TBI, MS, Parkinsons, etc.) but this report focuses on stroke.

## Robotic Therapy

One of the exciting developments in stroke rehabilitation is the emergence of rehabilitation robots.[3-4] Robots have a number of attractive inherent capabilities, ranging from the tireless ability to facilitate precise repetition of movement in multiple planes to the inclusion of integrated instrumentation, allowing kinematic analysis and feedback for performance. There have also been an incredible variety of robots that target impairment of the upper-limbs, lower limbs, or specific joints (such as the Anklebot[5]); devices that train movement unilaterally or bilaterally using exoskeleton systems or end-effector devices.

However, in parallel to the amazing technological developments, rigorous clinical testing is critical to evaluate safety and efficacy. To date there have been a number of pilot studies but very few large randomized controlled trials. The largest robot trial has been the **ROBOTICS study (Robots in Chronic Stroke)** conducted by the Department of Veterans Affairs.[6, 7] This study investigated the safety and efficacy of the MIT-Manus device (Figure 1) among 127 subjects with chronic upper extremity impairment following stroke. In addition to robot therapy, the study included an active treatment group that used conventional rehabilitation techniques. Although both groups showed improvement over the 36 week period of the study, there was no clear treatment advantage of robot over matched therapy using conventional methods.[8]

Most other smaller studies using upper-extremity devices have had similar results, such as with the T-Wrex (Figure 2).[9] A recent report has described ben-

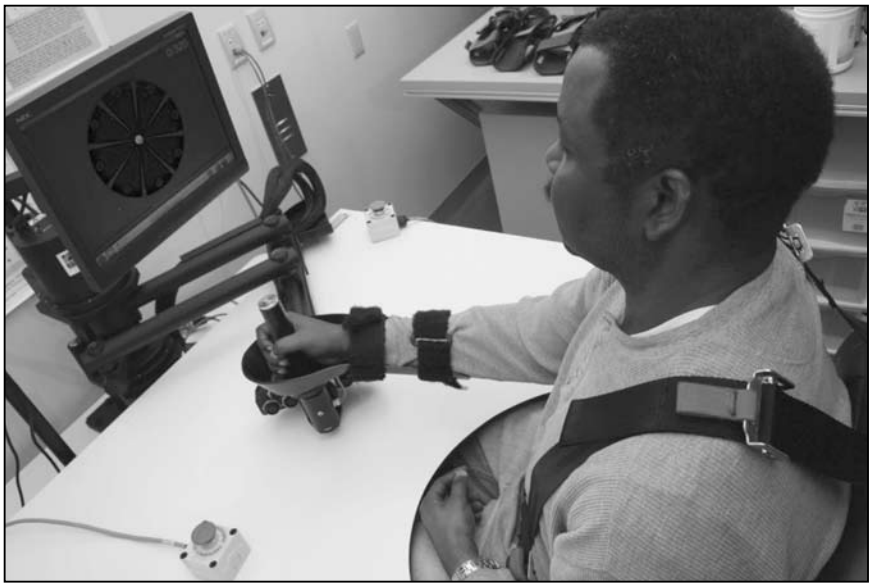

Figure 1: Manus Device

eficial results from the REO Therapy System for inpatients during the subacute timeframe.[10] Randomized studies focusing on the lower extremities using robotic-assisted gait training (Lokomat) (Figure 3) compared to conventional gait training, also have not shown advantages to the robot-based protocol on clinical outcomes.[11]

Nevertheless, rehabilitation clinical trial testing is evolving and it still may be a matter of identifying the optimal manner and environment to use robot technology. For example, enhanced use of feedback, or integration with virtual reality or telerehabilitation may be other promising strategies for robotic devices. Technology will continue to develop and robots should be viewed as tools with unique strengths and functions which must be optimized for their most appropriate clinical applications. Costs for robotic devices, which range from tens of thousands to $300,000, will also have to be greatly reduced in order for robots to be used commonly in clinical rehabilitation. In the broader scheme, robots like other tools must be used to their best advantage to investigate the critical questions of rehabilitation such as when to intervene with activity-based therapies, what are the appropriate doses and intensities, and how do we best track and predict treatment-responsiveness.

## Constraint-Induced Movement Therapy (CIMT)

This technique is based on the concept of *learned nonuse* advanced by Taub in the 1970s, and first examined in nonhuman primates,[12,13] in which use of an impaired limb is suppressed presumably by the finding that compensatory strategies are easier to utilize than relearning use of the affected limb. Taub postulated that *forced use* of the impaired limb and/or *prevention of use* of the non-affected limb could enhance functional recovery of the impaired limb. These principles were then adapted to human subjects with hemiparesis due to stroke.[14]

The classic CIMT paradigm involves intensive repetitive practice of use of the affected limb under the direct, continuous supervision of a therapist on a one-on-one basis for up to six to seven hours a day for at least two consecutive weeks while the better arm is prevented from being used (by using a sling or a mitt) for 90% of waking hours. Initial studies generally showed long-lasting benefits on various motor and real-world functional measures, but lack of vigorous control groups and small *N* were concerns. EXCITE, a multicenter, randomized, controlled trial, confirmed the effectiveness of the technique when applied rigorously in patients who are strongly motivated, have preserved cognition, and have some isolated movement present at the wrist before treatment.[15] Functional imaging studies suggest CIMT therapy is associated with cortical reorganization in areas involved in control of the affected limb. It is unclear if the mechanism of benefit is the mass practice of use of the affected limb alone vs. constraint of the other limb vs. both.

The classic paradigm, however, has not come into widespread use, as CIMT is expensive to administer due to the large amount of therapist time required and is generally not covered by insurance. In addition, some patients find it frustrating and overwhelming. The classic technique is limited to patients who fit criteria, which excludes more severely hemiparietic individuals.

As a result, several "**modified**" **CIMT** (**mCIMT**) trials have been run, involving less therapist time with more practice at home, less constraint on the other limb, and more liberal inclusion criteria. Some of these trials suggest that mCIMT paradigms could result in enhanced patient compliance, greater use, and be less expensive, while remaining effective.

In addition, the concept has been successfully applied to other stroke sequelae such as lower limb sensorimotor impairments and aphasia, as well as other diagnoses such as traumatic brain injury, spinal cord injury, focal dystonia, and phantom limb pain. It has also been applied in pediatric populations, particularly for cerebral palsy.

Classic CIMT is currently done only at highly specialized centers such as University of Alabama at Birmingham where the technique was developed. However, many therapists incorporate mCIMT into their treatment designs, and some centers are running mCIMT programs.

## Pharmacological Interventions

Another potential approach to enhancing spontaneous plasticity for restoration of poststroke neurological function is the use of medications.[16] Studies have been small, in selected populations and have had mixed results. Such studies are methodologically challenging, but the advent of functional imaging and genetic techniques may allow better characterization of involved neurotransmitter pathways which could in turn enhance the design of clinically useful studies.

It may seem intuitive that increasing the activity of a neurotransmitter system whose activity has decreased after a stroke, or vice versa, could be beneficial, but careful study is needed to ensure safety and to determine when agents will be most useful in which patient populations. In addition to direct clinical applications,


Figure 2: T-Wrex Device

studying the effects of such drugs could provide insight into the effects of stroke on specific neurotransmitter systems.

Most clinical studies have evaluated the effects of drugs on motor function and aphasia.

A discussion of several of these drugs provides a sense of the current state of knowledge. This is not a complete list of pharmacologic approaches to enhance stroke recovery. It is likely that medications will need to be used in combination with physical therapy or mass practice in order to produce a beneficial effect. Appropriate patient selection based on various parameters (e.g. clinical impairments, stroke size and location, and time elapsed since onset), is an additional challenge.

### d-Amphetamine and other stimulants

The theoretical action of amphetamine is its enhancement of the synaptic release of two neurotransmitters that support motor function, dopamine and noradrenaline. In a rat model, treatment with amphetamine, an enriched environment, and/or focused motor activity resulted in better motor function than controls, and treatment with all three showed the most robust recovery.[17]

Although some human studies have shown beneficial effects of d-Amphetamine, other studies have not. A 2007 Cochrane review concluded that its potential role in motor rehabilitation is unclear due to conflicting results in trials thus far.[18] Barbay and Nudo suggest that the better apparent results in animal vs. human studies may be attributable to uncertainty of optimal dosage and timing of administration.[19] A 2009 review of eleven trials noted an overall trend toward improved motor function, but raised concerns about safety particularly with respect to hemodynamic effects, and concluded that "No evidence exists at present to support the use of amphetamine after stroke."[20]

There have been a few studies of other stimulants in stroke. Methylphenidate (increases dopamine signaling), when combined with physical therapy, was shown to have a beneficial effect on motor outcomes and decreased depression. This drug has been better studied in TBI, with evidence that it may improve mental processing speed and reduce both ICU and hospital length of stay.[21]

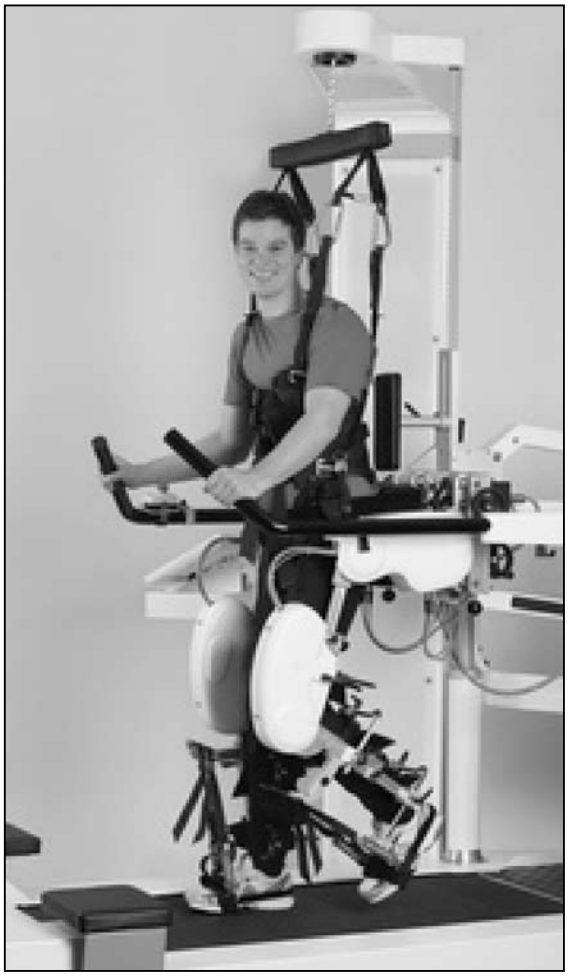

Figure 3: Lokomat device

### Selective Serotonin Uptake Inhibitors (SSRIs)

Studies in animal stroke models have suggested potential mechanisms by which SSRIs could enhance recovery.[22] In a study of severely disabled chronic stroke patients, ambulation and activities of daily living improved more in those treated with fluoxetine 20 mg daily than in those treated with 150 mg maprotiline (a tetracyclic antidepressant) or placebo.[23]

Another study found fluoxetine treatment to be associated with improvement in motor skills which correlated with changes in activation patterns on functional MRI.[24] In a small controlled trial, a single dose of citalopram 40 mg resulted in greater improvement in upper-limb dexterity but not grip strength in the affected, but not the unaffected, hand.[25] These studies suggest that SSRIs may have a measurable physiologic effect specific to areas important to post-stroke recovery of motor function, implying a mechanism other than antidepressant effects may be responsible for gains in motor function.

A larger ($N$ = 118) multicenter randomized controlled trial of fluoxetine in chronic stroke demonstrated significantly greater improvement in motor function in subjects treated with fluoxetine 20 mg daily compared to placebo, and the treatment was well-tolerated.[26]

Of note, preliminary retrospective reports suggest that SSRIs could increase the risk of stroke.[27] SSRIs are a promising class of drugs to enhance recovery of motor function in chronic stroke patients but further study is necessary to inform risk:benefit ratios before widespread clinical use can be considered.

### Phosphodiesterase type-5 Inhibitors (PDE-5I)

PDE-5I's are approved for use for the treatment of erectile dysfunction and idiopathic pulmonary arterial hypertension. However, the indications may broaden to treatment of cardiovascular, gastrointestinal, cutaneous, and neurologic disorders. They may be useful in Raynaud's phenomenon, heart failure, essential hypertension, and stroke.[28]

Cyclic **guanosine monophosphate** (**cGMP**), which increases with sildenafil citrate administration, increases neurogenesis, angiogenesis, and synaptogenesis in animal models of stroke.[29] A rat model of stroke suggests improvement in functional recovery and neuronal function due to modulation of microglial function and/or vasculature.[30]

An atypically good recovery without adverse effects was reported in a 41 year-old woman with locked-in syndrome due to a pontine stroke who was treated with sildenafil for several years.[31] The remarkable case of a 65-year-old man with chronic stroke whose residual bilateral inferior quadrantanopia reproducibly and

verifiably improved for three to seven days each time he took a dose of sildenafil 25 mg was recently reported. Functional MRI showed sildenafil-associated activations at the infarction periphery.[32] Silver et al found sildenafil to be safe when given for two weeks starting two to nine days after onset of mild to moderately severe stroke in a small trial.[33]

These and other preliminary reports, which suggest possible safety and efficacy along with functional imaging suggesting corresponding cortical effects, indicate that further investigation of the use of PDE-5I in rehabilitation after stroke is clearly warranted. Pfizer is now conducting a large study for this purpose (http://clinicaltrials.gov/ct2/show/NCT01208233).

### Levodopa (l-dopa)

Dopamine's essential role in motor pathways make l-dopa (which is converted to dopamine after crossing the blood-brain barrier) a good candidate as an intervention to influence motor recovery after stroke. However, study paradigms including single-dose and multiple daily dosing have produced mixed results so far.

A randomized, double-blind trial in 53 subjects 6-weeks poststroke found levodopa 100 mg once daily for three weeks was associated with greater motor improvement, which persisted at least three weeks, than placebo.[34] In a placebo-controlled crossover study of ten chronic stroke patients, motor performance was superior in subjects during a five-week course of once-daily levodopa.[35] However, similar studies did not replicate this finding.

Several studies have included the use of **Transcranial Magnetic Stimulation (TMS)** to investigate the physiologic effects of levodopa in chronic stroke patients.[36] TMS can be used to induce certain movements of a muscle group, for example of the thumb. Training and levodopa in some studies influence TMS-induced movements, which suggests that even single-dose levodopa may augment training-induced motor memory,[37] perhaps by modulating motor cortical excitability. Other TMS studies have shown no difference between levodopa and placebo.

Several studies have demonstrated amplification by levodopa of a beneficial effect of speech therapy on verbal fluency and repetition in aphasic patients, particularly in the setting of anterior lesions.[38] Similar studies have had conflicting results, however. Inconsistent results have similarly been found in studies of other medications' effects on aphasia recovery.

### Other medications

Piracetam, a derivative of GABA used in some parts of the world for myoclonus and cognitive enhancement (not available in the US) has been shown in several studies to improve aphasia in subacute stroke.[39] Its mechanism of action is unknown but it appears to increase brain glucose utilization and cellular metabolism. A PET study showed increased activity in areas supporting language only in a piracetam-treated group.

The acetylcholinesterase inhibitor donepezil improved aphasia after stroke on a measure of severity but not on a measure of day-to-day communication.[40]

Modafinil, known to improve fatigue in patients with multiple sclerosis, was shown in one study to improve fatigue in patients with brainstem or diencephalic strokes but not cortical strokes.[41]

## Mirror Therapy

V. S. Ramachandran and colleagues introduced Mirror Therapy as a method to reduce phantom limb pain due to amputation. Observing that painful phantoms are more likely to be present in individuals whose limbs were paralyzed before amputation, they hypothesized that the brain learned that the limb was paralyzed due to lack of proprioceptive feedback upon attempting to move the limb. This "learned paralysis" persists post-amputation, and pain results from the perception that the limb cannot be repositioned from a posture causing discomfort.[42] A "mirror box" was designed to reduce this "learned paralysis."

A vertical mirror is placed in front of the patient between the intact limb and the stump such that the patient sees in the mirror the reflection of the intact limb where the missing limb should be. The patient then performs movements with "both" hands, receiving visual feedback such that "movement" of the phantom limb is perceived visually, and the patient is able to "move" the phantom out of uncomfortable positions. Studies have shown some success in sustained reduction of phantom limb pain by this method.[43]

Use of mirror therapy has been extended to hemiparesis. Altschuler et al studied the effectiveness of mirror therapy in a crossover design in nine subjects with chronic stroke and hemiparesis.[44] The intervention consisted of 15 minutes of practice twice a day for four weeks with either a mirror or a transparent plastic sheet as a control; the following four weeks subjects were crossed over to the other treatment. Blinded observers rated improvement in more subjects during the mirror-treatment phase than during the control phase, and participants reported greater perception of benefit during the mirror phase. The authors suggested that visual perception of normal movement of the (virtual) affected arm compensates for decreased proprioceptive input from the (actual) affected arm resulting in improved function of the (actual) affected arm. Another proposed mechanism is improvement in premotor cortex recruitment as that area may be important for relating visual information to motor control.[45] It has also been suggested that mirror therapy may reduce learned disuse (the basis of CIMT, see above).[46]

Two randomized controlled trials of the use of mirror therapy for hand function after stroke are of interest. The first enrolled 40 inpatients three to 12 months after a stroke[47] and the intervention consisted of 30 minutes per day of mirror vs. sham therapy, five days per week, for four weeks, while continuing a conventional stroke rehabilitation program. The control group could not see the paretic limb as the nonreflective side of the mirror was used. After four weeks of treatment and at a six-month followup evaluation, the treatment group showed significant and lasting improvements in one measure of motor recovery and one measure of functional recovery, but no significant improvement in a measure of spasticity.

A blinded, randomized trial of home-based mirror therapy in subjects with chronic stroke demonstrated a shift in activation in the cortex of the affected hemisphere on functional MRI in subjects undergoing mirror therapy but not in controls.[48] The authors report this is the first study to suggest an association be-

tween mirror therapy and reorganization of cerebral cortex.

Mirror therapy is a promising technique requiring more study to determine which patients are most likely to benefit and at what period during recovery. As a simple, inexpensive, and patient-driven technique, it will have distinct advantages over other current and putative interventions if large controlled trials demonstrate meaningful effectiveness. In addition to phantom limb pain and poststroke paretic upper limbs, it may be useful in the treatment of patients with complex regional pain syndrome, neglect, and lower limb motor impairment.[49]

## Conclusions

Advances in basic neuroscience and technology are driving the development of novel interventions to enhance the natural recovery that occurs after stroke. These interventions range from pharmaceuticals, to elegant and inexpensive techniques such as CIMT and Mirror Therapy, to complex technologies including robotic devices and electrical or magnetic stimulation. Although determining appropriate patient populations and risk:benefit ratios is complex in rehabilitation settings, we have the capability to assess these techniques like never before with improved outcome measures and functional imaging. Neurorehabilitation specialists envision being able to offer stroke survivors a wider variety of therapies at various times during the recovery process that are validated to improve functional outcomes through cortical reorganization and other mechanisms. Exactly which interventions to offer which patients and in what sequence or combination remains to be determined.

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### Disclosure of off-label use of drugs

This article discusses off-label uses of medication.

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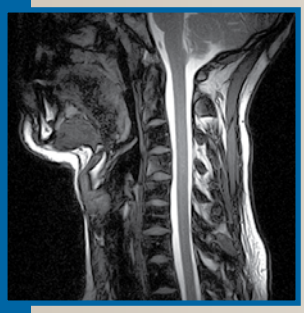

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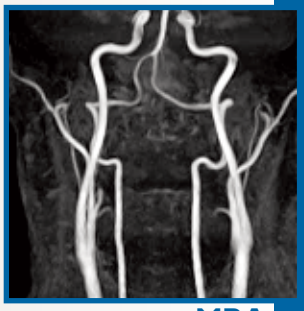

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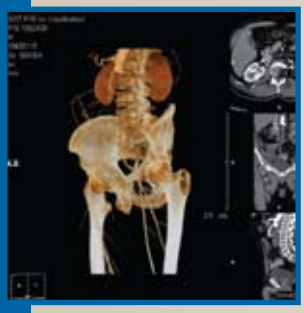

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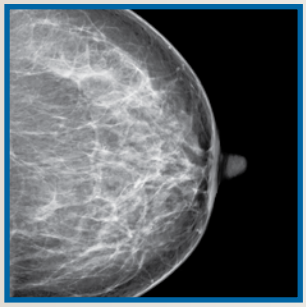

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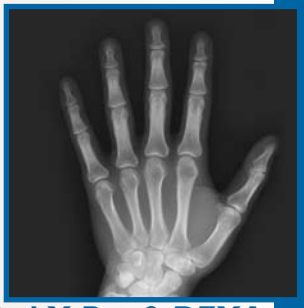

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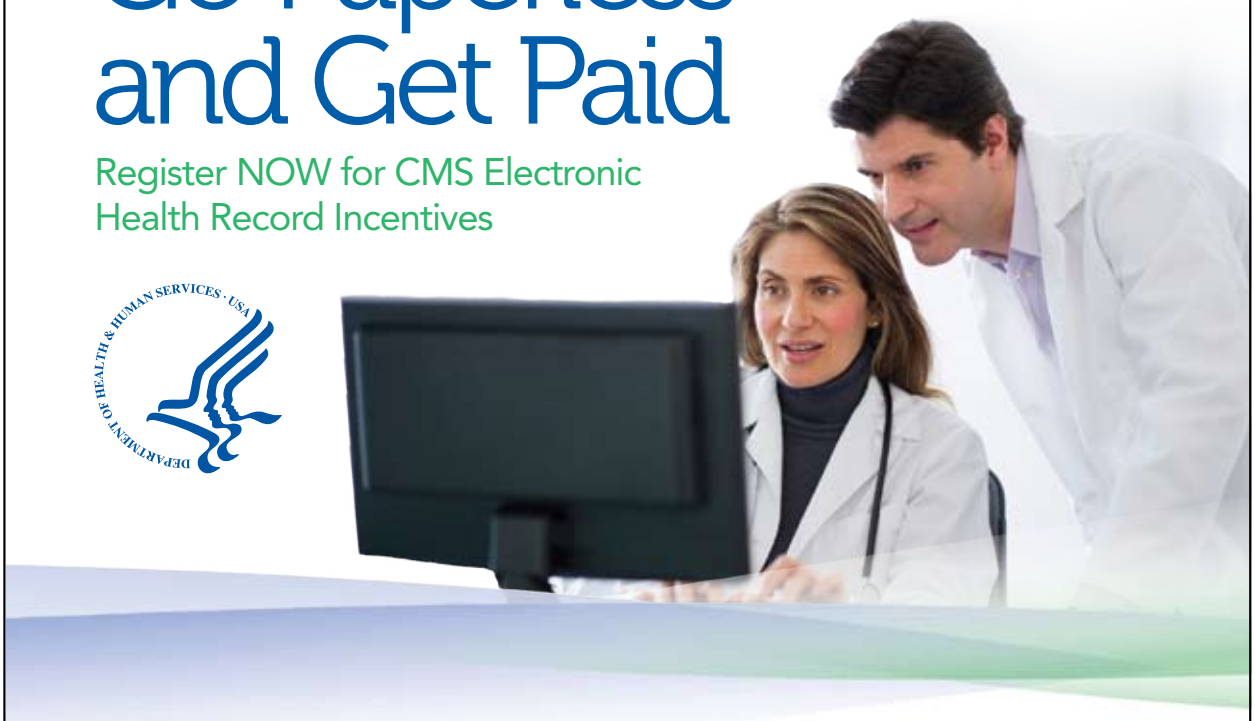

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# Primary Stroke Prevention and Community Education

*Michael Vecchione, DO*

**Stroke is the fourth leading cause of** death in the United States. Stroke affects almost 800,000 people in the United States each year with two-thirds of events being a first occurrence. Approximately 135,000 people die from stroke each year. In 2007, four of every 10,000 people in Rhode Island died from stroke-related complications.[1] According to the *Heart Disease and Stroke Statistics-2011 update:* A Report from the AHA, Rhode Island was third lowest in stroke mortality: 35 per 100,000 population.[2] This low rate in Rhode Island should not lend itself to complacency among health-care providers and patients. In addition to physical disability, the financial impact of stroke on patients, their families, and the healthcare system is significant.

## Stroke risk factors

Various clinical tools have been designed to assess a person's risk of having a first stroke. No one tool has been proven to be superior to all others. One such example is the **Framingham Stroke Profile** (**FSP**) tool. In the FSP tool, stroke risk factors [age, systolic blood pressure, diabetes, cigarette smoking, cardiovascular disease, atrial fibrillation, and **left ventricular hypertrophy** (**LVH**)] are assigned points. The tool predicts the ten-year probability of stroke based upon the number of total points.[3] Several easily accessible online stroke risk calculators can give clinicians and the general public an idea of ten-year stroke risk. These websites can be accessed through popular search engines by using the search terms "stroke risk calculator."

Stroke risk factors can be divided into two major classifications: non-modifiable and modifiable.

### Non-modifiable stroke risk factors

The non-modifiable stroke risk factors include age, gender, low birth weight, ethnicity/race, family history/genetic. As the name implies, these risk factors cannot be altered, and rates of stroke risk amongst them differ.

Stroke risk is lower in people ages 25-44 years old, while the risk of ischemic stroke and intracranial hemorrhage doubles for each successive decade after age 55.[3] Ischemic and hemorrhagic strokes tend to occur more often in men than in women. However, in women there is a bimodal pattern or increased stroke risk which includes women between the ages of 35-44 years old and women > 85 years of age. Possible explanations for this pattern include the use of oral contraceptives and pregnancies in younger women and a survival effect for older women, with more women alive at ages 85 and greater.[3] Low birth weight also appears to be a risk factor for stroke. Studies conducted in England, Wales, and the United States suggest that increased stroke risk in low birth weight infants may be due to lower socioeconomic status, malnutrition, and overall poor health. Babies weighing less than 2,500 grams have twice the risk of stroke when compared to babies weighing 4,000 grams.[3]

Race and ethnicity differences have also been recognized as an important stroke risk factor. By race and ethnicity, the risk of stroke is greatest in blacks and Hispanic Americans. Blacks had a 38% higher risk of strokes than whites in the **Atherosclerosis Risk In Communities** (**ARIC**) Study. Blacks tend to have a higher incidence of subcortical and lacunar infarcts which has been attributed to the higher incidence of hypertension in blacks when compared to whites.[4] Additionally, the death rate from stroke is twice as high in blacks when compared to whites, and in younger black populations (ages 45-64), it is three to four times higher.[4] Additionally, a family history of stroke leads to a an approximately 30% increased risk of stroke.[3] Potential factors contributing to this increased risk for stroke in a patient with a family history of stroke, geographic origin, include inherited genetic disorders, inheritance of other risk factors, shared cultural and environmental lifestyles within families, and the interaction between environmental and genetic factors.[4]

There are also inherited or genetic disorders that may increase a person's risk for stroke. These inherited disorders include **CADASIL** (**cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy**), **CARASIL** (**cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy**), **MELAS** (**mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke**), and a family history of intracranial aneurysms. Non-invasive screening for aneurysms is recommended when there are two of more affected first degree relatives with intracranial aneurysm or prior subarachnoid hemorrhage.[3] Inherited coagulopathies such as protein C. and S deficiencies, factor V Leiden mutations, and other factor deficiencies can lead to increased risk for venous thrombosis, and are often inherited in an autosomal dominant fashion.[3]

### Modifiable Stroke Risk Factors

By definition, these risk factors can be potentially altered through dietary changes, lifestyle changes and/or medications. The most common and well-documented modifiable risk factors include hypertension, cigarette smoking, diabetes, hyperlipidemia, atrial fibrillation, carotid stenosis, and more recently obstructive sleep apnea.

Hypertension is the single most important modifiable risk factor for ischemic and hemorrhagic stroke.[3] In a national survey of hypertension in the United States between 1999 and 2000, it was estimated that 65 million people in the United States suffer from this disorder.[3] As blood pressure increases, so does the risk for stroke. Reducing blood pressure alone offers one of the largest risk reductions (32%) when compared to other modifiable stroke risk factors. According to the **Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure** (**JNC-7**) guidelines, blood pressure should be < 140/90 in the majority of the population and < 130/80 in patients who are diabetics, although the ACCORD study did not find benefit of

blood pressures less than 120 systolic in diabetics.[5] The JNC-8 report is expected to be released in the fall of 2011. Blood pressure goals should be achieved by lifestyle modification as well as medications.[3] Meta-analyses of studies looking at different blood pressure medications have shown no definitive evidence to date that one class of blood pressure medication offers any additional special protection against stroke over another class.[3] However, beta-blockers do not prevent stroke as well as other agents despite achieving similar reductions in blood pressure, in part because the risk of diabetes is higher with beta-blockers.[6, 7]

Cigarette smoking has been identified as a potent risk factor for stroke, doubling the risk for ischemic stroke.[3] The stroke and cardiovascular risk reduction seen in people who stop smoking can occur rapidly and quickly approaches but never reaches that of nonsmokers.[3] According to the new AHA/ASA guidelines, a 50% reduction in stroke can be seen within one year of a smoking cessation.[3] Therefore, older patients and long-term smokers should not feel that they are too old or have been smoking too long to stop. Smoking cessation should be the goal of every patient, young or old. Smoking increases the risk for ischemic and hemorrhagic stroke in women on oral contraceptives compared to women who do not smoke. The risk for intracranial hemorrhage is somewhat more inconsistent.[3]

Diabetes has numerous adverse health effects on multiple organ systems in people, including the cerebrovascular system. The risk for stroke from diabetes ranges from two to six times higher.[3] The most recent statistics taken from the CDC website, report approximately 24 million people in the United States suffer from diabetes. In 2007, it was reported that 17.9 million Americans suffered from diabetes.[3] In Rhode Island, it is estimated that 6-8% of the population suffer from diabetes.[1] The American Diabetic Association website reported that in 2004 68% of patients with diabetes died from heart disease and 16% of patients with diabetes died from stroke**.** Consequently, a large number of diabetic patients die from the #1 and #4 most common causes of death. Improved glycemic control reduces other microvascular disease complications of diabetes.[3] To date**,** intensive glycemic control has not been shown to reduce the risk of a first stroke in diabetic patients. In fact, targeting glycated hemoglobins below 6% results in increased mortality over five years and does not lower stroke risk.[8] Current recommendations suggest a target of less than 7%. Management of other stroke risk factors becomes more important in diabetics. Trials such as **Collaborative Atorvastatin Diabetes Study (CARD)**[9] and **Treating to New Targets (TNT)**[10] study showed that the use of a statin medication in a patient with the diabetes reduces the risk of stroke by 48% and 40%, respectively. The AHA/ASA guidelines state that statin medications should be used in diabetic patients but the addition of a fibrate is not useful for decreasing stroke risk. The benefit of aspirin for primary stroke risk reduction has not been demonstrated for patients with diabetes but should be considered in those patients with high cardiovascular disease risks.[3]

Dyslipidemia has been shown in most epidemiological studies to be associated with a higher risk for ischemic stroke. One meta-analysis estimated that statins can reduce the risk of all strokes by approximately 20%.[3] The **National Cholesterol Education Program (NCEP)** states that in general, an optimal LDL would be < 100 and near optimal levels would be between 100-129 mg/dL. HMG-CoA reductase inhibitor medications are recommended for primary prevention of stroke in patients with CAD or other high risk of populations.[3] The AIM-HIGH trial was recently stopped early because a futility analysis showed that high-dose extended release niacin added to simvastatin did not confer an advantage compared with simvastatin alone.[11] Further, the ACCORD lipid study found that the addition of fenofibrate to simvastatin did not further reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone.[12] In the ILLUMINATE trial, torcetrapib, an investigational agent, raised HDL and reduced triglycerides but increased the rate of cardiovascular events.[13]

**Atrial fibrillation (AF)** is associated with a five-fold increased risk for ischemic stroke. Four other clinical features have also been found to increase the risk for stroke in patients with AF: prior stroke or TIA, advancing age, hypertension, and diabetes.[3] Active screening for AF in patients >65 years old using EKG is recommended. Anticoagulation with warfarin (INR 2.0-3.0) in patients thought to be at significant risk for stroke with a low bleeding risk is recommended. Antiplatelet therapy using aspirin is recommended in patients who are thought to have a low risk of stroke related to their AF and/or in patients who may have an increased risk of bleeding/bleeding complications on warfarin.[3] A more recent study showed that for AF patients with high risk for stroke deemed not a candidate for warfarin therapy, the combination of clopidogrel plus aspirin is recommended.[3] From the **RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy)** trial[14], dabigatran etexilate, an oral thrombin inhibitor, has been approved for the prevention of stroke in patients with AF.

**Asymptomatic carotid stenosis (ACS)** has been identified as a risk factor for first-time stroke. Patients with ACS should be screened for other modifiable stroke risk factors, and appropriate stroke risk modification should be initiated for each of these risk factors.[3] It is reported that with "best medical therapy" today, the annual risk of stroke from ACS is < 1%.[3] Surgical or other intravascular treatments should be decided after thorough review of the degree of carotid artery stenosis (> 60% by angiography, > 70% by Doppler, > 80% by CTA or MRA) patient' s life expectancy, comorbidities, risks versus benefits, and a low complication risk (< 3%) by the treating physician(s).

Recently, it has become recognized that **obstructive sleep apnea (OSA)** is an independent risk factor for stroke. It is recommended that OSA patients be treated although its effectiveness on reducing stroke still remains unknown.[3] It is recommended that patients with risk factors for developing OSA be screened with a detailed history and physical examination along with identification and treatment of other stroke risk factors.

Other potentially modifiable stroke risk factors include sickle cell disease, oral contraceptive use, migraine headaches, metabolic syndrome, physical inactivity, alcohol consumption, drug use, elevated glycoprotein-a, hypercoagulable disorders, hyperhomocysteinemia, and infection and inflammation.

Aspirin is not useful in preventing a first-time stroke in a patient with a low stroke risk. Aspirin should be considered in patients with a high risk for cardiovascular events, which includes strokes, where the benefits outweigh the risks. From the **Women's Health Initiative (WHI)**, aspirin 81-100 mg every other day can be useful for preventing a first-time stroke in women >65 years old and in whom the risk of bleeding is outweighed by the potential benefit.[3] However, a large meta-analysis expressed uncertainty about aspirin in primary prevention.[15]

## Community Education

Because stroke risk factor identification and modification can lead to a reduction in stroke, a number of organizations have initiated campaigns to educate healthcare providers and the public about stroke risk factors and warning signs and symptoms. Only a small percentage of patients suffering from stroke recognize the warning signs and symptoms. This contributes to a low number of people coming to the hospital within the time window to receive tPA. In a study of 163 patients, 39% were not able to identify a single sign or symptom of stroke and, more concerning, higher-risk patients (> 65yo) were less likely to do so.[16]

The F.A.S.T. media campaign was started by the Massachusetts Department of Health in 2006 and adopted by the Rhode Island Department of Health to educate the public about stroke. This media campaign uses a simple four letter acronym **F**ace-**A**rm-**S**peech-**T**ime and an animated video that comes in four different languages: English, Spanish, Portuguese, and Khmer/Cambodian.

The Power To End Stroke campaign, which began in 2006, was developed from the AHA/ASA with a mission to reduce stroke and the risk of stroke by 25% by 2010. This campaign targets blacks, given their increased risk for heart disease, hypertension, and stroke.

Give Me 5 for Stroke is a campaign started in 2007 by the Stroke Collaborative to educate health-care providers and patients about stroke. The Stroke Collaborative is made up of different groups including the American Academy of Neurology, American College of Emergency Physicians, and the AHA/ASA. Their stated goals are to combine resources and increase stroke awareness among the public.

The **National Stroke Association (NSA)** has a web site dedicated to stroke education and advocacy. The Stroke Advocacy Network website is designed to improve quality care for stroke survivors by helping people communicate with legislators about stroke. The NSA also publishes *StrokeSmart Magazine*, a book called *Hope: The Stroke Recovery Guide*, and the *Brain Alert Newsletter* all of which are designed to provide further information about stroke to healthcare providers and the public. The National Stroke Association also has a website called Brainiac Kids dedicated to providing stroke education to children in a manner that encourages learning.

The Rhode Island Heart Disease and Stroke Prevention Steering Committee, made up of more than 60 organizations and individuals, developed the RI HDSP State Plan 2009 to reduce the impact of heart disease and stroke on the state. Certified Primary Stroke Centers, of which there are currently four in Rhode Island, are required to provide community education as part of their certification. Additionally, some hospitals have stroke support groups that meet regularly with stroke survivors and/or their caregivers to provide continuing education and support.

## Conclusions

While stroke continues to have a major impact on patients, their caregivers, and their community, continued efforts at stroke risk factor identification and management along with stroke education may provide one of the best opportunities for reducing the impact of this disease. These goals can only be achieved by active participation from healthcare providers, the public, and legislators.

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# Secondary Stroke Prevention in 2011: An Update on Available Options

*Shelly Ozark, MD, and Brian Silver, MD*

**The array of medical interventions for** secondary stroke prevention has dramatically increased in the last decade. The approach is multi-factorial and includes not only pharmacological, e.g., anti-platelets or anti-coagulants where appropriate, reductions in blood pressure, cholesterol lowering agents, but also lifestyle e.g., smoking cessation, diet, and exercise. This review will focus on these recent advances.

## Hypertension

### Caution when treating blood pressure in the first week after stroke

Treatment of hypertension after stroke should be considered two-fold: the first week after stroke and the period after the first week. There was considerable debate about whether blood pressure should be lowered in the first week but the recent SCAST trial found that lowering of blood pressure with candesartan in the first week (mean blood pressure of 147/82 versus 152/84 on placebo, p<0.0001) neither reduced recurrent stroke nor mortality.[1] In fact, functional outcomes at six months, as measured by the modified Rankin scale, appeared to be worse in candesartan-treated patients (adjusted common odds ratio of a poor outcome 1.17, p=0.048). Thus, aggressive treatment of blood pressure within the first week after stroke should be avoided.

### Blood pressure is the single most important modifiable risk factor for stroke

Nevertheless, blood pressure should be lowered in the long-term. A systematic review found that chronic reduction of blood pressure in patients with prior ischemic or hemorrhagic stroke or transient ischemic attack reduced secondary stroke by 24%, nonfatal stroke by 21%, myocardial infarction by 21%, and total vascular events by 21% over a period of two to five years.[2] No effect was seen on vascular or all cause mortality. The reduction in stroke was related to the difference in systolic blood pressure between treatment and control groups (P=0.002). All classes of drugs appeared to be effective except for beta blockers which did not show a difference compared with placebo.

### The importance of medication selection for blood pressure lowering

Though beta blockers have been used for many years for reduction of blood pressure, multiple randomized trials show inferiority of beta blockers for stroke prevention compared with other agents. A Cochrane systematic review of 13 randomized trials including 91,561 participants found a trend towards worse outcomes with beta blockers when compared to calcium-channel blockers, renin-angiotensin system inhibitors, and thiazide diuretics.[3] Another Cochrane review concluded that available studies supported first-line use of low-dose thiazide diuretics, ACE inhibitors, and calcium channel blockers but not high-dose thiazide diurectics or beta blockers.[4] Among first-line agents, diuretics may be best followed by calcium channel blockers and then ACE inhibitors and angiotensin receptor blockers.[5]

### The ideal blood pressure has yet to be defined: Studies are ongoing

The ultimate target for blood pressure reduction is uncertain. JNC7 recommends a blood pressure of less than 140/90 in most patients and less than 130/80 in diabetics and those with chronic kidney disease.[6] The latter target was recently challenged by the ACCORD findings which found no difference in outcomes in diabetic patients allocated to a target of less than 120 mmHg systolic compared with those treated to less than 140 mmHg systolic.[7] The SPS3 study, scheduled to have final results in 2012, will evaluate the difference in outcomes among patients with small subcortical strokes allocated to blood pressures of less than 130 mmHg systolic versus those allocated to blood pressures of 130-149 mmHg systolic with or without clopidogrel added to aspirin.[8]

## Hyperlipidemia

### Statins are beneficial in patients with ischemic stroke

The **SPARCL trial** (**Stroke Prevention by Aggressive Reduction in Cholesterol Levels**) showed that lowering **LDL** (**low density lipoprotein**) levels reduces the risk of subsequent stroke.[9] In this study, 4,371 patients with a ischemic stroke, hemorrhagic stroke, or TIA within the previous one to six months were randomized to 80 mg of atorvastatin or placebo. Important exclusion criteria in this study included a history of coronary artery disease and LDL levels that were not in the range of 100-190 mg/dL. Approximately 2% of all enrolled patients had hemorrhagic stroke as the qualifying event. As compared with patients receiving placebo, patients who were assigned to atorvastatin had a 2.2% absolute risk reduction of recurrent stroke over five years and a 3.5% absolute risk reduction in major cardiovascular events over five years. There was an increased risk of hemorrhagic stroke with atorvastatin use (2.3% over five years with atorvastatin versus 1.4% over five years with placebo). Nevertheless, the reduction in ischemic stroke events far outweighed the occurrence of hemorrhagic stroke events. The precise target for LDL reduction is uncertain however, the degree of LDL reduction correlates with the degree of reduction in recurrent stroke.[10, 11]

### Caution is advised when considering statins in patients with hemorrhagic stroke

In regards to statin treatment of patients with hemorrhagic stroke, a recent analysis suggested that the risks of continued use of statins in that population outweighed potential benefits.[12] Avoiding statins yielded a life expectancy gain of 2.2 quality-adjusted life-years compared with statin use in such patients. The authors concluded that statin use should be avoided in patients with intracerebral hemorrhage.

### Niacin and fibrates may not be beneficial for reducing risk of stroke

Attempts to lower triglyceride levels and increase HDL may be beneficial for patients who have had a stroke or TIA. In the **Veterans Affairs HDL Intervention Trial (VA-HIT)**, 2,531 men with coronary artery disease were assigned to gemfibrozil 1200 mg/day or placebo.[13] The gemfibrozil group had a reduced risk of stroke over five years compared to placebo (4.6% versus 6.0%, respectively). Similarly, in an older study among patients with coronary artery disease, niacin demonstrated a reduction in stroke over five years compared with placebo (2.3% versus 2.9%).[14] However, recent trials targeting HDL and triglycerides have not been positive. In the AIM-HIGH trial, high-dose extended release niacin was added to simvastatin and produced the expected effect of raising HDL and lowering triglycerides, however the study stopped early because a futility analysis showed that clinical outcomes were not significantly affected.[15] In the ACCORD lipid study, the addition of fenofibrate to simvastatin did not further reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone.[16] Finally, in the ILLUMINATE trial, torcetrapib, an investigational agent, also raised HDL and reduced triglycerides but increased the rate of cardiovascular events.[17]

## Lifestyle Modification

### Smoking

Both active and secondhand exposure to tobacco smoking increases the risk of stroke.[18] The average number of quit attempts by former smokers is approximately six.[19] Approximately 2% of patients who are counseled to stop smoking during a single office visit will do so and not relapse after one year.[20] Nicotine replacement therapy results in 13% of patients being smoke free. At this time, there is insufficient data to support acupuncture, acupressure, laser therapy, and electrostimulation for smoking cessation.[21] Pharmacotherapy that has been shown to increase the chances of smoking cessation include bupropion[22] and varenicline.[23, 24]

### Alcohol consumption

While chronic heavy alcohol use increases the risk of ischemic stroke,[25, 26] light to moderate consumption may be somewhat protective,[26, 27] though there may be a slightly increased risk of stroke immediately following alcohol consumption.[28] Daily consumption of small amounts of alcohol, defined as one drink per day for women and two drinks per day for men, may reduce platelet aggregation and raise HDL.[29] While patients who drink heavily should be encouraged to cut back or quit, there is insufficient evidence at this time that non-drinkers should be advised to start drinking alcohol.

### Physical activity

Physical activity should be encouraged in all patients as part of both primary and secondary prevention of stroke. In terms of primary prevention, moderate degrees of exercise may reduce the risk of stroke by about 20% while high levels of activity may cut stroke risk by about 30%.[30] Though the beneficial role of exercise in secondary prevention has not been validated through randomized clinical trials, exercise is widely held as likely in helping to improve physical disability as well as reduce the risk of further events. For patients with post-stroke disability or deconditioning, physical therapy can provide a structured environment for increasing activity appropriately. Outside of such programs, patients should be counseled to maintain as active a lifestyle as possible. Randomized clinical trials show that robotic therapy and virtual gaming are also helpful in improving physical function.[31] Patients who are given a written prescription for exercise are more likely to engage in physical activity than those who have not received a prescription.[32]

## Treatment of stroke patients with atrial fibrillation

### Anticoagulation in patients with stroke and atrial fibrillation should be favored, when feasible

There is robust evidence that patients with atrial fibrillation and stroke should be started on anticoagulation, if feasible.[33] In patients with atrial fibrillation, warfarin reduces the risk of stroke by approximately 60% while antiplatelets reduce the risk by 20%. Assuming an annual recurrent event rate of approximately 10% in patients with atrial fibrillation and stroke, the absolute risk reduction is substantial.

### Novel treatment options for patients with stroke and atrial fibrillation

Warfarin was first patented in 1941 as a rodenticide and approved for therapeutic use in humans in 1954. It inhibits the enzyme epoxide reductase which results in disruption of vitamin K metabolism.[34] The most significant advance in secondary stroke prevention for atrial fibrillation in the last year was the introduction of a monitoring-free alternative to warfarin. Dabigatran is a competitive direct thrombin inhibitor which prevents the conversion of fibrinogen to fibrin. Previously available in Europe and Canada for the prevention of deep vein thrombosis in orthopedic surgery patients, dabigatran was approved for use based on results of the **Re-LY (Randomized Evaluation of Long term anticoagulant therapy)** trial.[35]

The RE-LY trial compared the efficacy and safety of open-label adjusted-dose warfarin (goal INR of 2 to 3), versus fixed-dose dabigatran high (either 150mg twice daily or 110 mg twice daily). 18,113 patients with a history of both atrial fibrillation and at least one additional stroke risk factor were randomly assigned to one of the three treatment arms. The concomitant use of anti-platelet agents such as aspirin or clopidogrel was permitted. The primary outcome in the trial was the time to clinically evident stroke or systemic embolism, including pulmonary embolism and myocardial infarction.

At entry, the mean $CHADS_2$ score was 2.1. While both the 110mg and 150mg twice daily doses of dabigatran were found to be non-inferior to warfarin for prevention of stroke, the 150mg twice daily dose was, in fact, superior to warfarin. Patients randomized to warfarin had at 1.69% per year rate of the primary study outcome of stroke or embolism, as compared to 1.11% per year for patients randomized to 150mg of dabigatran. Patients in the adjusted-dose warfarin arm were in the target range (INR 2-3) 64% of the time. A post-hoc analysis indicated that dabigatran 150 mg twice daily was superior to warfarin regardless of percentage time in the therapeutic range.[36] Patients in the warfarin arm had a rate of major bleeding events of 3.36% per year, with a hemorrhagic stroke rate of 0.38% per year, while patients receiving dabigatran 110 mg twice daily had a major bleeding rate of 2.71% and hemorrhagic stroke rate of 0.12%. Patients receiving dabigatran 150 mg twice daily had major

bleeding rates of 3.11% and hemorrhagic stroke rate of 0.10% per year.

In October 2010, the FDA advisory board approved the 150mg dose of dabigatran. However, the FDA did not approve the 110 mg dose because their analysis failed to show a group for whom this dose would be beneficial.[37] The main point of the decision was that major bleeding which was not intracranial was not weighted as important as stroke.

There is no known reversal agent for dabigatran if a patient does experience hemorrhage. The medication should be stopped if bleeding occurs. Other interventions such as fresh frozen plasma and other coagulation factor concentrates are of uncertain utility.

For patients presenting with acute ischemic stroke in whom tPA is being considered, there is one case report of a patient who was treated seven hours after last ingestion of dabigatran without subsequent hemorrhage.[38] Because the half-life is 12-17 hours, patients may be considered for treatment 12-24 hours after the last dose although no large scale studies are available at this time.

If a patient is transitioned from warfarin to dabigatran, the recommendation is to wait until the INR is below 2.0 before starting dabigatran. Dabigatran's onset of action is one hour after ingestion. Although no monitoring is required for patients taking dabigatran, its effect can be determined by testing an **ecarin clotting time (ECT)** or a **thrombin time (TT)**. Both the ECT and TT have linear results with respect to dabigatran plasma concentrations. The **activated partial thromboplastin time (aPTT)** can also be used although its correlation with dabigatran levels is nonlinear. The INR should be used since it is unaffected by dabigatran.

In regards to clearance for surgery and other procedures, the manufacturer's prescribing information suggests that for most patients with normal creatinine clearance, stopping dabigatran one to two days prior to most invasive procedures is appropriate; three to five days for patient with reduced creatinine clearance may be required. Dabigatran should be restarted post-procedure as soon as clinically possible. Dabigatran cannot be crushed and given via naso-gastric tube.

Though dabigatran use is cost-ffective from a societal perspective (reference), at an individual level, it is more expensive than warfarin (cost comparison on drugstore.com). For patients who are stable on warfarin, the recommendation is to maintain warfarin treatment.

One final note concerns the packaging of dabigatran. Given in blister packs (which is common in Europe), the drug is useful for at least one year. However, when administered as pills in a bottle (which is common in the United States), exposure to air results in rapid deterioration of the drug such that it may not be effective after 30-90 days. We recommend that the medication be prescribed in blister packs for this reason. Most pharmacies are able to accommodate this request.

### Other direct thrombin inhibitors

Two other direct thrombin inhibitors are under consideration by the FDA at the time of this writing. The Rocket-AF trial showed non-inferiority of the Factor Xa inhibitor rivaroxaban when compared to warfarin in the prevention of stroke in patients with atrial fibrillation.[39] An on-treatment analysis showed a 21% reduction in the risk of stroke and non-CNS embolic events, though an intention-to-treat analysis failed to show superiority of the drug. Bleeding rates were found to be statistically equivalent between the two drugs. The AVERROES trial showed that apixiban was superior to aspirin for the prevention of stroke (1.6% per year versus 3.7% per year) in patients who were unwilling to take warfarin in the setting of atrial fibrillation or were deemed unsuitable.[40]

### Alternative strategies for patients with stroke and atrial fibrillation who cannot be anticoagulated

The **Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W)** which compared the use of warfarin with INR 2.0-3.0 to aspirin 75-100 mg plus clopidogrel 75 mg was stopped early because the rate of ischemic stroke was substantially higher in the combination antiplatelet group (5.60% per year versus 3.93% per year).[41] Therefore patients who have atrial fibrillation and are candidates for anticoagulation should preferentially receive warfarin or a direct thrombin inhibitor.

Some patients are deemed unsuitable for anticoagulation for a number of reasons including frequent falls. For these patients, the ACTIVE-A trial showed that the combination of clopidogrel plus aspirin was mildly superior to aspirin alone for reducing the occurrence of stroke (2.4% per year versus 3.3% per year).[42] The risk of major bleeding was higher when clopidogrel was added to aspirin (2.0% per year versus 1.3% per year).

## Other aniplatelet agents

In the **Cilostazol Stroke Prevention Study 2 (CSPS-2)**, cilostazol appeared to be more effective than aspirin in preventing recurrent stroke (yearly rate of 2.76% versus 3.71%) with a lower rate of hemorrhage (0.77% versus 1.78%).[43] It has not been FDA approved for this purpose yet, and may not be approved at all because the study took place outside the United States (in Japan).

## The hazards of long-term dual antiplatelet therapy

An increased risk of bleeding with dual antiplatelet therapy was found in The **Management of ATherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischemic stroke (MATCH)** study which showed that the addition of aspirin to clopidogrel had no net benefit in preventing stroke over clopidogrel alone but greatly increased the risk of bleeding.[44] Likewise, in the CHARISMA study,[45] the combination of aspirin and clopidogrel had no advantage over aspirin monotherapy for the prevention of cardiovascular events, but did increase the risk of bleeding. Taken together, these studies indicate that monotherapy should be the treatment of choice for long-term secondary prevention in patients with non-atrial fibrillation stroke.

Though the MATCH trial showed no benefit of dual anti-platelet therapy over clopidogrel alone over the long term, the role for short term combination therapy following stroke is still under investigation. The ongoing **Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT)** trial is comparing clopidogrel plus aspirin versus aspirin alone for 90 days following stroke.[46]

## Conclusion and future directions

Though stroke continues to be common, advances in medical treatment have substantially reduced the risk of recurrence. Using a strategy of blood pressure

control, lipid modification, aggressive treatment of atrial fibrillation, and lifestyle intervention (i.e., diet and exercise), the array of treatments has evolved beyond which antiplatelet is best. Continuing advances in the neurological sciences (including genomic therapy) will further reduce the likelihood of a second event.

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### Disclosure of Financial Interests

Brian Silver, MD, has served as a consultant for Abbott Vascular and as a defense expert in medical malpractice cases of stroke.

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# The Importance of Stroke Units

*Karl Meisel, MD, and Brian Silver, MD*

## Stroke Units Improve Patient Outcomes

Stroke is the fourth leading cause of death and a leading cause of disability in the United States.[1] Over the past two decades advances in the acute treatment of stroke using thrombolytics has improved patient outcomes. Progress has also occurred in secondary stroke prevention including additional antiplatelet agents, improved blood pressure control, statin use, better treatment of atrial fibrillation, and management of carotid stenosis. A recent study found that nearly two-thirds of Medicare patients who had a stroke died or were rehospitalized within one year.[2] Stroke units have been adopted by many centers for the treatment of acute stroke. This review will examine the science behind the stroke unit and its organization.

## The role of the stroke unit

The ideal organization of hospital stroke care for risk factor evaluation and rehabilitation has been debated as far back as the 1950s.[3] Historically, the debate centered on whether patients with strokes were best served in a dedicated stroke unit compared to a general medical ward. More recently, trials have compared more versus less organized stroke services. The stroke unit is defined as including specialized personnel caring for stroke patients in a discrete ward. Conceptually, the model for this plan is similar to that of a coronary care unit which is widely accepted as the standard for care of patients with coronary artery disease. Under this general definition, an intensive model of an acute stroke unit would include continuous monitoring, high level of nursing care with possible life support services. The semi-intensive model would be similar but lacking life support, whereas non-intensive would have none of these resources. Additionally, there are rehabilitation stroke units that accept patients after an initial delay of about a week and comprehensive stroke units that combine both acute and rehabilitation stroke care.[4]

Initial studies from the 1970s suggested that intensive care unit management of stroke patients might not be beneficial.[3] However, since the 1980s, multiple trials have found significant benefits to an organized stroke unit to concentrate resources with associated quality and cost effectiveness.[5] It is believed that nurses who are specially trained in stroke care can better monitor and educate patients. Moreover, rehabilitation services like speech, physical, and occupational therapy would be concentrated and specialized to assist with the care of this unique population. Finally, social workers or case managers who arrange the post hospital care from stroke units are more experienced in coordinating appropriate community resources.[4]

## The impact of stroke units

A comprehensive review of the literature regarding the impact of stroke units has found an overall benefit. A Cochrane meta-analysis of 31 trials found a reduced odds of death at a median of one year [odds ratio (OR) 0.86 (CI 0.76-0.98, P = 0.02)].[4] The benefit was even stronger if institutionalization (OR 0.82 CI 0.73 – 0.92, P = 0.0006) or dependency (0.82 CI 0.73 - 0.92, P = 0.001) were the measured outcomes. These 31 trials comprised 6939 subjects; 16 of the 31 studies compared stroke wards with general medical wards, four compared mobile stroke teams with medical wards, six compared mixed rehabilitation wards with medical wards, while the remaining compared stroke wards against mixed rehabilitation (five trials), comprehensive treatments wards (two trials), and mobile stroke teams (one trial). Sixteen trials were randomized and ten were blinded to final outcome. The final odds ratios did not change when trials were excluded because they lacked proper randomization, were not blinded, or did not have a pre-fixed interval outcome time for final analysis. The benefit of stroke unit assignment continues for at least five (three trials) and ten years (two trials).

Since the Cochrane report, the benefit of stroke units continues to be further validated. An Australian multi-center observational study of 17,659 admissions for ischemic stroke found a significant decrease in mortality (13.8% to 10.5%, p <0.001), increase of discharges to home (38.8% to 44.5%), and decrease in discharges to nursing homes (6.3% to 4.9%).[6] These differences remained statistically significant after controlling for demographics and indicators for a poor prognosis. Additional evidence that support stroke units versus general medical wards comes from a Canadian study of 3,631 patients. The authors found the thirty day mortality was 10.2% versus 14.8% (P<0.0001) with a number needed to treat of twenty-two.[7]

Since the 1990s studies have begun comparing more organized discrete stroke wards with less organized stroke services like a mixed rehabilitation ward or mobile stroke team. The Cochrane review concluded that a patient in a stroke ward was more likely to survive the acute hospitalization and return home living independently.[4] However, the strength of comparing alternative stroke services is based on only eight trials, therefore definitive conclusions are lacking. Further studies that are randomized, blinded and include long term follow-up are needed to determine what type of acute stroke ward organization yields the best patient outcomes and at what cost.

## Length of stay

There is a modest reduction in the length of stay when comparing stroke unit care to an alternative organizational structure. Data was available from twenty-six trials for the Cochrane review, but was limited by heterogeneity of how hospital stay was calculated. Therefore instead of directly combining trial data the authors used a random-effects model of statistical analysis. They concluded that stroke units reduced time of stay by an equivalent of four days (range two to six).[4] An additional Canadian study published after the Cochrane meta-analysis evaluated one center's experience and found the average length of stay in a stroke unit was 15 days versus 19 days in a general ward. The odds that stroke patient would stay in hospital

greater than seven days was reduced by 30% (p<0.0001).[8] There have been no such studies in the United States.

## Cost effectiveness analysis

The cost effectiveness of stroke unit care is uncertain. The few studies that have addressed this topic were conducted in a nationalized health care system and are difficult to translate to the United States. One report from England suggested that a home primary care model would be more cost effective until the quality-adjusted life-year reached about 60,000 pounds.[9] However, other studies have found stroke units are cost effective.[10,11] The cost advantage described in some investigations is attributable to reduced complications from stroke such as aspirations, shorter lengths of stay, decreased risk of recurrent strokes, decreased mortality, and better functional outcome.[10-12] A study in France found the difference between general wards and a stroke unit was 1,359 euros per year of life gained without disability.[11] A recent report compared a strategy of combining stroke unit with early home care versus stroke unit alone and found a positive cost effectiveness due to years of life saved.[13] The majority of the cost for a stroke unit is the initial investment of infrastructure. Also the operating costs are dependent upon the level of services provided, such as the number of nurses, rehabilitation specialists, and specialty equipment used for monitoring or rehabilitation.

## Do all strokes need the same level of care?

Another area of uncertainty is whether all stroke patients' benefit from a stroke unit or just the more severely affected. A randomized study found that stroke units only benefited those patients with large vessel infarcts compared to those with small vessel lacunar infarcts who were treated with a mobile stroke service in a medical ward. The study found that small vessel stroke patients treated in a stroke unit had increased length of stay and more resources were used.[14] The Cochrane review conducted a subgroup analysis that showed no significant reduction of mortality in mild stroke patients (OR 0.92; CI 0.64-1.32; P < 0.05), but did conclude that they reduced risk of dependency (OR 0.75; CI 0.58-0.96; P = 0.02).[4] Therefore, further investigations are needed to help determine whether various stroke subtypes should be treated in different hospital units to maximize resources and overall outcomes.

## Conclusion

Stroke units, defined as discrete locations within a hospital that provide coordinated care involving therapists, nurses, social workers, and neurologists with supportive technologies, has significant benefit to patient outcomes. These benefits include reduced mortality and morbidity, and improved functional independence. The issue of stroke units will become even more important as the population ages.

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Brian Silver, MD, has served as a consultant for Abbott Vascular and as a defense expert in medical malpractice cases of stroke.

Karl Meisel, MD, and/or their spouse/significant other have no financial interests to disclose.

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# The 'Golden Hour' Treatment of Acute Ischemic Stroke

*Arshad Iqbal, MD*

**Data on the incidence of stroke,** collected by the American Heart Association, indicate that in the United States there is a stroke about every 40 seconds and a person dies of stroke about every four minutes. At the moment, there are three to four million Americans who are stroke survivors. Each year, there are roughly 795,000 new strokes in the United States. The death rate is approximately 30% of all stroke victims.

## A Conceptual Framework for Earlier Treatment of Stroke

Studies of cerebral blood flow and metabolism show that flow in brain region supplied by an occluded artery is variably reduced depending in part on the distance of the region from the stroke epicenter, and that flow in much of these regions is sufficient to maintain viability for some period of time as evidenced by correlative measurements of local oxygen and glucose metabolism. The brain regions that are threatened but viable are termed the "ischemic penumbra" and the time this penumbra could remain viable is termed the 'therapeutic time window" The more profound the reduction in blood flow the briefer this window becomes.[1]

Saver calculated that in patients experiencing a typical large vessel ischemic stroke, 1.9 million neurons, 14 billion synapses and 7.9 miles of myelinated fibers are destroyed each minute. Compared with the normal rate of neuronal loss in aging brain, the ischemic brain ages 3.6 years each hour without treatment.[2]

## Clinical Data in Support of Earlier Treatment Times

Results of acute ischemic stroke treatment trials have taught us that in order to maximize therapeutic benefit we must treat our patients early; the earlier the better. In the landmark NINDS study those who were treated in zero to 90 minutes had lesser disability at three months than those treated between 91-180 minutes. More specifically, treatment with rtPA initiated within 90 minutes of symptom onset was associated with an odds ratio of 2.11 (95% confidence interval, 1.33 to 3.55) for favorable outcome at three months as compared with placebo. In comparison, the odds ratio for good outcome at three months for treatment with rtPA initiated within 90 to 180 minutes was 1.69 (95% confidence interval, 1.09 to 2.62).[3] Results of NINDS study were closely matched by at least one subsequent large clinical trial.[4]

Lansberg et al looked at the pooled data set of the first six major randomized acute stroke trials of intravenous tissue plasminogen activator with a goal to identify the **number needed to benefit** (**NNB**) and **number needed to harm** (NNH). They found that NNB was 3.6 for patients treated between zero and 90 minutes, 4.3 for treatment between 91 and 180 minutes, 5.9 for treatment between 181 and 270 minutes, and 19.3 for treatment between 271 and 360 minutes. The NNH estimates for the corresponding time intervals were 65, 38, 30, and 14. The analysis clearly showed that earlier treatment was linked to a greater chance of benefit and a reduced chance of harm. It also showed that treatment up to 4.5 hours resulted in more benefit than harm.[5]

## Emerging concept of The Golden Hour

Prehospital delay continues to contribute the largest proportion of delay in treatment.[6] Lack of awareness of stroke symptoms is a key component of that delay. The CDC analyzed data from an optional module of the 2005 **Behavioral Risk Factor Surveillance System** (**BRFSS**) survey that was used in 13 states and the District of Columbia (DC). The findings were as follows: All five stroke warning symptoms were identified by 43.6% of respondents; 18.6% were aware of all stroke warning symptoms and knew that sudden chest pain is not a stroke warning sign; 38.1% were aware of all stroke warning symptoms and would first call 9-1-1 if they thought that someone was having a heart attack or stroke, and 16.4% were aware of all five stroke warning symptoms, knew that sudden chest pain is not a stroke warning symptom, and would call 9-1-1 if they thought that someone was having a heart attack or stroke. Awareness of all five stroke warning symptoms and calling 9-1-1 was higher among whites (41.3%), women (41.5%), and persons at higher education levels (47.6% for persons with a college degree or more) than among blacks and Hispanics (29.5% and 26.8%, respectively), men (34.5%), and persons at lower education levels (22.5% for those who had not received a high school diploma).[7]

Patients receiving treatment within the first 60 minutes of symptom onset, termed the Golden Hour, have the greatest opportunity to benefit from recanalization therapy.

An analysis of data from hospitals participating in the American Heart Association and American Stroke Association Get With the Guidelines Stroke initiative found that 30,220 patients (28.3%) arrived in emergency room within 60 minutes of stroke symptom onset, 33,585 (31.7%) arrived between 61-180 minutes and 42,846(40.1%) patients arrived >180 minutes. Compared with patients arriving at 61-180 minutes, golden hour patients received thrombolytic therapy more frequently (27.1% vs. 12.9%), but experienced a significantly longer **door to needle time** (DTN) – 90.6 vs. 76.7 minutes. Only 18.3% of golden hour patients received thrombolytic therapy in less than 60 minutes from arrival.[8] An inverse relationship was found between time remaining in the treatment window and time to treatment i.e., those with the greatest amount of time left to treat had the longest DTN time while those who had the least amount of time left had the shortest DTN times.

GWTG-Stroke data indicate that patients arriving within 60 minutes of stroke onset accounted for one in eight of all ischemic stroke patients at GWTG hospitals. Projected nationally, these numbers translate to more than 55,000 patients presenting to acute care hospitals within the first 60 minutes of ischemic stroke onset.

Since early time of presentation is critical to early start of therapy, a public health priority is to increase even further the proportion of acute ischemic stroke patients presenting within the first 60 minutes after onset. The two most powerful

predictors of early arrival are 1) stroke severity on NIH stroke scale and 2) arrival by ambulance rather than private vehicle.

GTWG-stroke hospitals currently constitute only 23% of US hospitals. The treatment numbers are less robust in non-participating hospitals. In the California Acute Stroke Pilot Registry, of 374 patients with ischemic stroke, 88 (23.5%) arrived at the emergency department within three hours of symptom onset, of whom only 16 (4.3%) received thrombolytic treatment. The authors derived hypothetical treatment rates for thrombolysis based on observed rates of eligibility and treatment. If all patients with known onset times had called 911 immediately, they calculated the overall rate of thrombolytic treatment within three hours would have increased from 4.3 to 28.6%. If all patients with known time of onset had arrived within one hour and been rapidly assessed, 57% could have received treatment.[9]

## Measures That May Reduce Treatment Times and a National Program Targeting Improvement

With compelling evidence that our efforts to reduce stroke related disability and improve outcome in many stroke patients is intimately tied to early intravenous therapy, let's look at what measures seem to work.

> It all must start with Community education with focus on awareness of stroke symptoms, knowledge of stroke risk factors and utilization of emergency response system – 911.[10]

A national quality improvement initiative of the American Heart Association and American Stroke Association to improve the care of acute stroke is underway. Termed Target: Stroke, the goal is to achieve a door to needle time within 60 minutes in at least 50% of ischemic stroke patients.

The following measures are based on American Stroke Association sponsored Target: Stroke campaign's 'Best Practice Strategies':

- Advance hospital notification by EMS.
- Rapid ED triage protocol and stroke team notification
- Single call activation system – A single call should activate the entire stroke team
- Stroke tools – A Stroke Toolkit containing clinical decision support, stroke specific order sets, and other stroke tools should be available in the ED and utilized for each patient
- Rapid acquisition and interpretation of brain imaging – Scanner clearance as soon as ED is made aware of incoming patient, It is essential to initiate a CT scan (or MRI) within 25 minutes of arrival and complete interpretation of the scan within 45 minutes of arrival to exclude intracranial hemorrhage prior to administration of IV rt-tPA
- Rapid laboratory testing. Recent studies suggest it is not necessary to wait for INR results of patients in whom coagulopathy is not suspected
- Mix the tPA medication ahead of time. Genentech has a stated policy of replacing the drug free of charge if it is mixed but not given in time-critical emergency situations like acute stroke
- tPA should be readily available in the ED or CT scanner (if scanner is located away from the ED). Dosing charts and standardized order sets will facilitate timely administration
- Team based approach – Collaboration in developing treatment pathways among physicians, nurses, pharmacists, laboratory administrators, department of neurology and radiology has been shown to be effective in reducing time to treatment in stroke
- Continuous data collection to drive system improvement. Accurately measuring and tracking the hospital's door to needle times equips the stroke team to identify areas for improvement and take appropriate action. A data monitoring and feedback system includes Get With The Guidelines® – Stroke Patient Management Tool which creates a process for providing timely feedback and comparisons to national averages.

## Conclusion

In summary, the last decade of stroke research has highlighted the importance of rapid treatment of acute stroke. Improving treatment times is possible and can be accomplished through a variety of system interventions.

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# Sexual Orientation and Health Risk Behaviors among Rhode Island Public High School Students, 2009

*Bruce Cryan, MBA, MS, and Donald Perry, MPA*

**Nine percent (9%) of public high school students responding** to the 2009 Rhode Island **Youth Risk Behavior Survey (YRBS)** reported that they were **lesbian, gay, bisexual or unsure (LGBU)** of their sexual identity. This percentage represents approximately 4,600 students statewide. The authors examined whether there were any differences in health risk behaviors and exposures for this population versus their heterosexual peers.

## Methodology

In the spring of 2009, 3,213 Rhode Island high school (grades 9-12) students participated in the YRBS. The YRBS is a biennial, sample survey of public high school students administered nationally and in over 60 states and muncipalities. The **Centers for Disease Control and Prevention (CDC)** developed the YRBS to monitor risk behaviors related to the major causes of mortality, disease, and injury in the U.S.[1] Survey data are weighted to be representative of the statewide population of public secondary school students.

The 2009 YRBS asked Rhode Island students the following question: "Which of the following best describes you? 1) heterosexual; 2) lesbian or gay; 3) bisexual, or 4) not sure." Their responses were then parsed into two categories, students self-reporting either #1 (heterosexual), or #s 2, 3 or 4 (LGBU).

The authors reviewed 21 behavioral measures related to violence and injuries, mental health, tobacco, alcohol and other drugs, sexual behavior, weight, and physical activity. As sample survey data can only produce estimates, confidence intervals (i.e., value ranges) were calculated around each observed percentage representing where the actual population value would lie 95% of the time. For each risk measure, the authors compared whether there was any overlap in the confidence intervals for LGBU versus heterosexual students. The lack of any overlap is an indication that there was a statistically significant difference between the two groups.[2]

## Results

Demographically, LGBU students were more prevalent among females (11% versus 6% for males), students with physical disabilities (19% versus 7% for the non-physically disabled), and students with emotional problems or learning disabilities (22% versus 7% for the non-emotionally disabled). LGBU students were also more common among low academic performers (mostly 'D & F' grades) than high performers (mostly 'A & B' grades) at 14% versus 7%, respectively.

Compared to heterosexual students, LGBU students were at greater risk for 17 of the 21 risk behaviors in this study. Violence was much more common among LGBU students. (Figure 1) They were one and a half times more likely to have been in a physical fight, and almost twice as likely to have been a victim of dating violence. In addition, the forced intercourse rate was almost three times higher for this group compared to heterosexuals. In contrast, injury risks were mixed for LGBU students. Although there was a significantly higher rate of not wearing seat belts, the LGBU group had a statistically comparable rate for riding with a driver who had been drinking alcohol. (Figure 1)

LGBU students were at greater risk for mental health issues than heterosexual students. (Figure 1) For example, compared to heterosexual students, LGBU students were almost twice as likely to report feeling sad or hopeless and were over three times more likely to report they had planned to commit suicide. Most

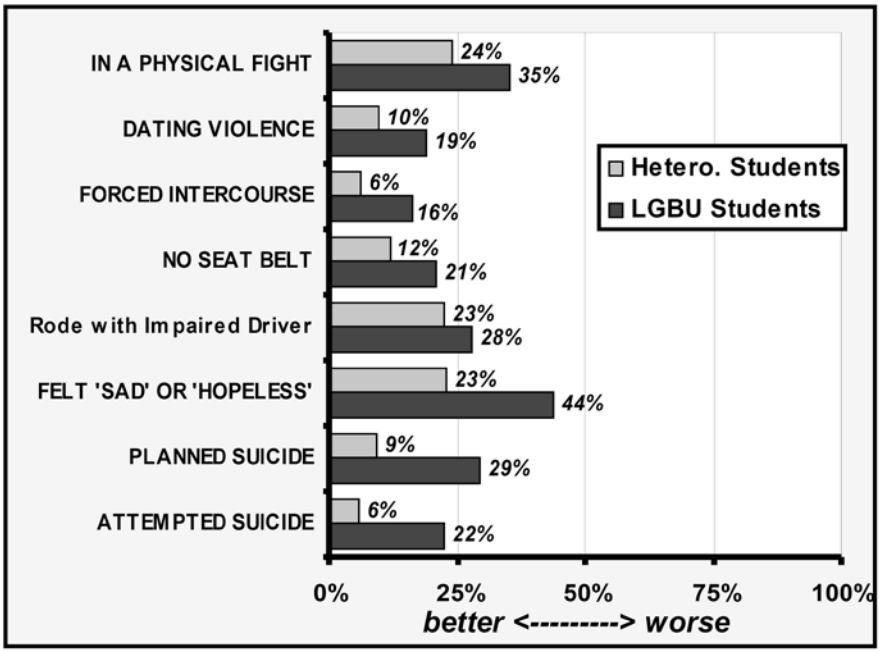


Figure 1. 2009 Violence, Injury, and Mental Health Risks by Sexual Orientation (significant differences are in CAPS)

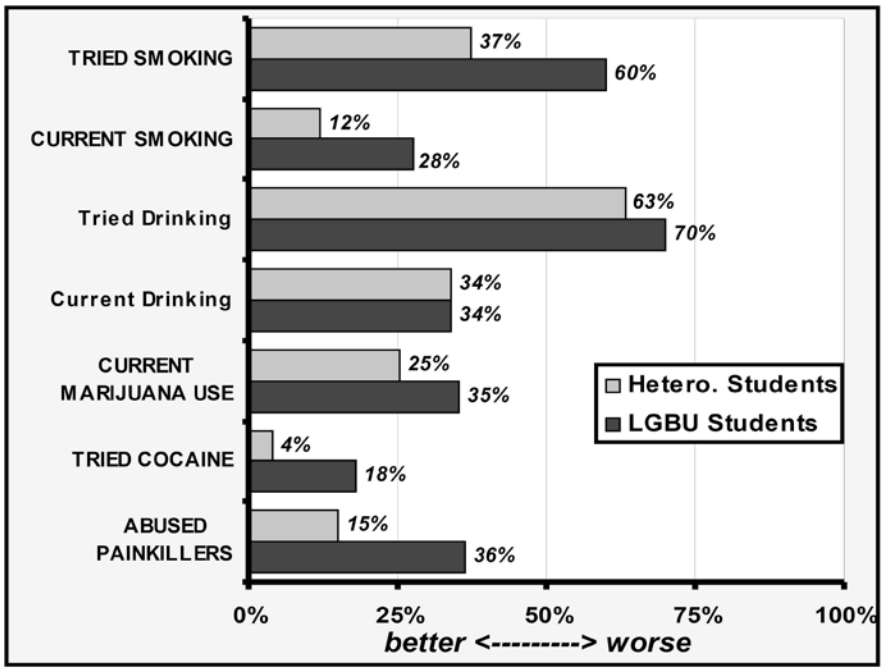


Figure 2. 2009 Substance Abuse Risks by Sexual Orientation
(significant differences are in CAPS)

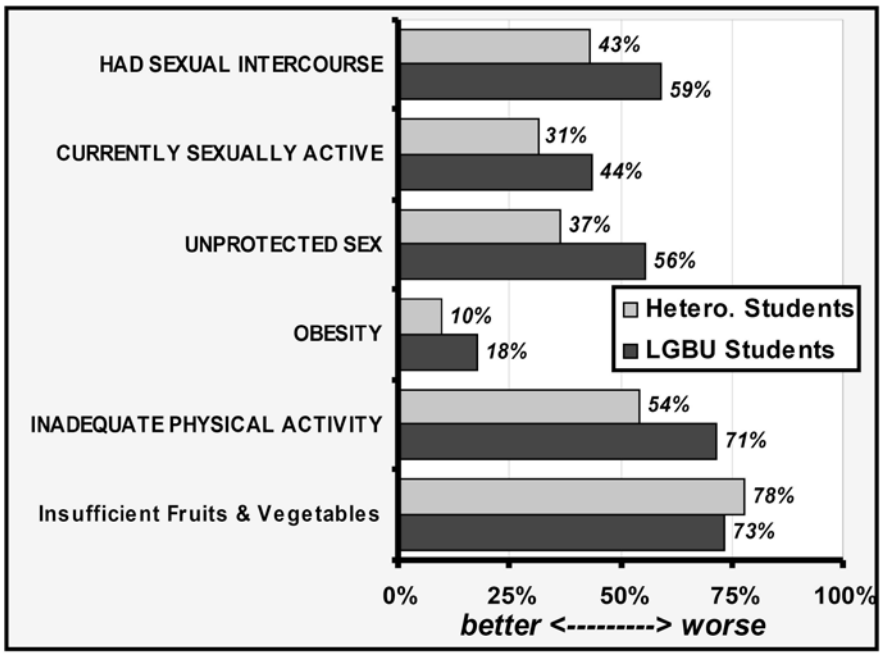


Figure 3. 2009 Other Health Risks by Sexual Orientation
(significant differences are in CAPS)

telling, however, was an attempted suicide rate (22%) that was almost four times higher for this vulnerable population compared to heterosexual students (6%).

Tobacco related risks were also higher for LGBU students compared to heterosexual students, where more of them had tried smoking at least once (60% versus 37%), and over twice as many were current cigarette smokers (within past 30 days). (Figure 2)

In contrast, LGBU students were not at greater risk for alcohol use. (Figure 2) The rates for students that had tried drinking were statistically comparable as were the rates for current drinking (within past 30 days). However, abuse of other drugs was higher among LGBU students. (Figure 2) They were more likely to be current marijuana users (within past 30 days), and over four times as likely to have ever tried cocaine. Furthermore, over twice as many LGBU students had abused prescription painkillers.

LGBU students were also at greater risk for sexual activity than heterosexual students. (Figure 3) They were 1.4 times more likely to have ever had sexual intercourse or to be currently sexually active (past three months). Sexually active LGBU students were also one and a half times more likely to have had intercourse without a condom compared to their heterosexual peers.

Physical activity and weight issues were generally more prevalent for LGBU than heterosexual students. (Figure 3) The rate of inadequate exercise among LGBU adolescents was much higher, which most likely contributed to their obesity rate being nearly twice that for heterosexuals. In contrast, insufficient consumption of fruits and vegetables was not appreciably different between the two population groups. (Figure 3)

## Discussion

LGBU high school students are clearly a vulnerable population displaying a higher prevalence of health risk behaviors across most categories. Dating violence (one in five LGBU students), forced sexual intercourse (one in six students), attempted suicide (over one in five students), and unsafe sex (over half of sexually active students) are particularly disturbing. Equally noteworthy is that more than one in three LBGU students had abused painkillers or were current marijuana users and nearly one in five had ever tried cocaine.

Reducing health disparities, such as those described above, requires concerted effort in identifying at-risk groups and their particular vulnerabilities. Physicians and other healthcare providers play an important role through identification and referrals. Effective interventions for LGBU youth, such as physical and mental health counseling and referrals, can help them to change negative behaviors over which they have control (e.g., smoking, unprotected sex), and avoid exposure to other

risk situations in which they are essentially victims (e.g., rape, dating violence). This may be especially true for females, low academic performers, and the disabled who are more likely to identify as LGBU.

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# Information for Contributors

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Contributions report on an issue of interest to clinicians in Rhode Island: new research, treatment options, collaborative interventions, review of controversies. Maximum length: 2500 words. Maximum number of references: 15. Tables, charts and figures should be submitted as separate electronic files ( jpeg, tif, or pdf). Each submission should also be accompanied by a short (100-150 words) abstract.

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Readers share their perspective on any issue facing clinicians (e.g., ethics, health care policy, relationships with patients). Maximum length: 1200 words.

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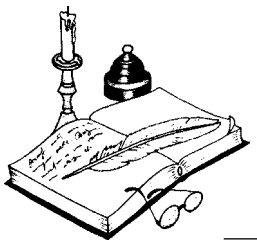

# Physician's Lexicon

## The Harsh Vocabulary of Intemperance

**"And Noah began to be a husbandman,** and he planted a vineyard; and he drank of the wine and was drunken." Thus we learn from Genesis (9:20-21) the Scriptural origins, the antiquity of alcoholism; and we learn further that intemperance was an impediment to mankind even before mankind learned to be fruitful, to multiply and replenish the earth.

Alcoholism, as a human burden, is widespread; and the descriptive words of alcoholism are similarly abundant and varied.

The word, alcohol, descends from the Arabic *al-kuhl* meaning the antimony and earlier from the Hebrew, *kahal*, meaning a fine powder such as antimony (used as an eye shadow and often called *kohl*; and by inference, something intense or spirited.)

An older medical term for alcoholism was dipsomania, derived from the Greek, *dipsa*, meaning thirst (for any fluids), and *mania*, also Greek, for madness. Dipsosis, a term often used in tropical medicine texts, defines thirst in general; and adipsia, the pathological absence of thirst. *Dipsosaurus dorsalis* (the Sonoran desert iguana), sometimes called the thirsty lizard, is a common creature to the hot Mojave desert lands.

Oenomania, a rarely employed diagnosis for chronic alcoholism, takes advantage of the Greek root for wine, *oeno-*, as employed in such terms as oenology, the study of wines; oenanthic, the odors of wine; oenophile, a lover of wine; and Oenone, in Greek mythology, the nymph-wife of Paris.

Temperance (and intemperance) are from the Latin, *temperans*, meaning to moderate, control, regulate, or diminish (as in the Scottish hymn, "Temper my spirits, Oh Lord".) The French infinitive, *tremper*, means to soak and sometimes dilute with water (and inferentially, therefore, lessen the action of the wine.).

An inebriant, a drunkard, is from the Latin, *inebriatus,* meaning an intoxicated human. The English word, brio, meaning vivacity, vigor, aliveness is also derived from the same root.

The street vocabulary for alcoholism is vast and multilingual, including such distasteful descriptives as barfly, souse, boozer (from a Middle Dutch, *busen*, meaning to carouse) , rummy, vodka (from the diminutive of an older Russian word, *voda*, meaning water) and whisky-head (the word, whisky, derives from the Gaelic, *usquebaugh*, meaning, literally, the water of life.)

– Stanley M. Aronson, MD

Rhode Island Department of Health
Michael Fine, MD
Director of Health

# Vital Statistics

Edited by Colleen Fontana, State Registrar

## Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

| Underlying Cause of Death | Reporting Period | | | |
|---|---|---|---|---|
| | December 2010 | 12 Months Ending with December 2010 | | |
| | Number (a) | Number (a) | Rates (b) | YPLL (c) |
| Diseases of the Heart | 222 | 2,257 | 214.3 | 3,112.0 |
| Malignant Neoplasms | 193 | 2,294 | 217.8 | 5,956.5 |
| Cerebrovascular Diseases | 41 | 457 | 43.4 | 684.5 |
| Injuries (Accidents/Suicide/Homicide) | 66 | 637 | 60.5 | 10,113.5 |
| COPD | 47 | 511 | 48.5 | 475.0 |

| Vital Events | Reporting Period | | |
|---|---|---|---|
| | June 2011 | 12 Months Ending with June 2011 | |
| | Number | Number | Rates |
| Live Births | 971 | 11,702 | 11.1* |
| Deaths | 716 | 9,926 | 9.4* |
| *Infant Deaths* | (3) | (65) | 5.6# |
| *Neonatal Deaths* | (3) | (65) | 5.6# |
| Marriages | 742 | 6,144 | 5.8* |
| Divorces | 300 | 3,332 | 3.2* |
| Induced Terminations | 361 | 4,054 | 346.4# |
| Spontaneous Fetal Deaths | 44 | 651 | 55.6# |
| *Under 20 weeks gestation* | (41) | (570) | 57.4# |
| *20+ weeks gestation* | (3) | (79) | 6.8# |

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,053,209. (www.census.gov)

(c) Years of Potential Life Lost (YPLL).

***Note:*** *Totals represent vital events that occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.*

* Rates per 1,000 estimated population
\# Rates per 1,000 live births

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## Ninety Years Ago, December, 1921

William Newton Hughes, AM, MD of the State Hospital for Mental Diseases studies the effects of ne month's luminal treatment of idiopathic epilepsy in 30 select cases. After introducing his range of subjects, Dr. Hughes reports that most patients respond to the treatment noting sleepiness, dizziness, and headaches and, with some cases, an increase in quarrelsome behavior. Overall, he reports a decrease in frequency and severity of seizures in the subjects compared to previous months and to the same month in the previous year, suggesting, too, a possibility that some of the positive effects could have been made moreso had it not been for the controlled three-grain dosage of the study group. He finishes by stating that no serious symptoms were observed that could be directly linked to the luminal.

Banice Feinberg, an intern at the State Hospital for Mental Diseases discusses psychometric methods for practicing physicians in terms of family practice, school, workplace, and in gauging mental disease. The author puts forward the benefits of testing, with some experience, as an additional diagnostic tool for physicians, and stresses the need to promote, in addition to physical hygiene, mental hygiene.

An editorial bemoans the presence of intellectual snobbery in the field of medicine—particularly such behavior as it comes from young interns recently of large hospitals who believe their knowledge of most recent advances in medical sciences makes it unnecessary for them to consult with the common general practitioner. The author emphasizes that the field of medicine is too broad for anyone to assume they can know the hundredth part of it all or that "his brother with less conspicuous advantages must be an ignoramus."

William R. White, MD, celebrates the ninetieth birthday of William J. Burge with a 38-verse poem that begins: "Two most distinguished given names / Are borne by you, friend William James / And when we add the 'Burge, M.D.' / It's surely 'Sir to you,' say we."

## Fifty Years Ago, December, 1961

A summary report prepared by the Washington Office of the American Medical Association states in regard to radioactive fallout: "The Public Health Service said that radioactive fallout levels in the United States up until early November from the new series of Soviet nuclear explosions 'do not warrant undue public concern' nor initiation of any special public health actions."

Robert L. Berger, MD, Joseph Doll, MD, and Orland F. Smith, MD, look at cases of congenital atresias of the gastrointestinal tract. While there have been vast improvements in anesthesia and fluid therapies in treating intestinal atresias, the overall outlook is still grim with the leading causes of death being malnutrition with dehydration and peritonitis.

An editorial points to a piece of news datelined Washington, DC, in a Dublin newspaper that states that "since October, 1948, United States medical examination centers have rejected more than a million men as physically unfit for military service as volunteers or national servicemen. In the past year they have been turning away more than 1,000 a month who would have passed if they had kept themselves in good physical shape. President Kennedy has urged schools to pay more attention to cultivating physical fitness."

Five Rhode Island physicians were inducted as Fellows of the American College of Surgeons, entitling them to the designation FACS following their name. The recipients of this honor were: Stephen J. Hoye, MD, of Pawtucket, Thomas F. Head, MD, Rudolph W. Pearson, MD, and Mendell Robinson, MD of Providence, and James F. Martin, MD, of Westerly.

## Twenty-five Years Ago, December, 1986

Seebert Goldowsky. MD, revisits the topic of the Rhode Island Medical Society's library from the previous issue, noting the library's gradual decline while at the same time celebrating its richness. He quotes Richard J. Wolfe, a distinguished authority on the field of rare books and manuscripts, "In summation, I found that Rhode Island Medical Society owns a small but very fine historical collection, one which is on par with some universities conducting programs, including graduate programs, in medical history; that such a collection has been built up over a century-and-a-half reflects the collecting interests and tastes of some of Rhode Island's outstanding medical personalities—Usher Parsons and Charles V. Chapin, for example—and that such a collection could not be assembled again at this late date, and, therefore, great care should be exercised in reaching a decision regarding its future. I would like to see this collection remain in Rhode Island to serve as a resource for the teaching and study of medical history there."

Starting in January 1987, the Rhode Island Medical Society will publish Check-Up, a new newsletter. Check-Up will replace the current RIMS newsletter and will not be part of the *Rhode Island Medical Journal*. The new publication is the result of extensive discussions of the RIMS Council concerning the communications mechanisms of the Society. The timeliness of the current newsletter has often been questioned. By separating it from the Journal, the production schedule will be improved.

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