Interventional modalities for the prevention and management of acute ischemic stroke : current evidence and future directions : a clinical review

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Dedication

This article is dedicated to my family, friends, and my fiancé who have provided me with the love and support needed to achieve my goals.

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Introduction

Stroke is the third leading causes of death in the U.S., with approximately 795,000 people experiencing a stroke each year. As a highly prevalent condition, stroke carries a high socioeconomic burden. According to the American Stroke Association, stroke is responsible for 1 in every 17 deaths in the U.S. and requires an estimated cost of $68.9 billion for 2009. The ischemic stroke patient in the U.S. is suspected to accrue a mean lifetime cost of approximately $140,000, which includes longterm care, following an event (Lloyd-Jones et al., 2009). For the past two decades physicians and scientists have been working to unveil new medical modalities to lower the catastrophic number of yearly strokes. Currently when patients present with acute ischemic stroke, treatment options are limited. In 1996, the FDA approved tissue plasminogen activator (t-PA) to be used intravenously within 3 hours of acute ischemic stroke onset. Among the limitations of intravenous thrombolysis are 1) the short time window for initiation of treatment, 2) low revascularization rates, and 3) increased risk of life-threatening hemorrhage. These factors likely account, in large part, for t-PA being administered to only 2 to 3% of acute stroke patients nationally (Alberts et al., 2000; Molina & Saver, 2005).

With approximately 25% of strokes being recurrences, attention must also be focused on prevention (Rosamond et al., 2008). Currently stroke prevention is focused on medically reducing thromboembolism with antiplatelets and anticoagulants, and with reducing cholesterol levels and blood pressure. Anticoagulation is indicated for patients with increased risk of stroke such as atrial fibrillation, prosthetic heart values, and possibly for patent foramen ovale (PFO). Even when anticoagulation has shown significant benefit, it still poses a definite bleeding risk which results in a limited number of candidates for the therapy. Not only are many not eligible for use of anticoagulants, the therapy has shown limited effectiveness in those that do qualify for

use of anticoagulation. Due to the enormous burden of stroke, this paper will explore interventional procedures which have the potential to lengthen the therapeutic window and improve efficiency in the acute setting, as well as those which prevent stroke recurrence.

The purpose of this clinical review is to evaluate advanced treatment options available for acute ischemic stroke and secondary prevention in order to enable healthcare providers to determine the most appropriate therapy for their patients and to determine if existing data is sufficient to alter the current standard of care. My objectives are to provide information on interventional treatment modalities including: neuroprotection with hypothermia, endovascular delivery of thrombolytics, and clot retrieval. As for prevention, I will discuss advanced interventional treatment for the following conditions which carry high risk for recurrent stroke: atrial fibrillation, atrial septal defects (including patent foramen ovale and atrial septal aneurysm), and carotid atherosclerosis (specifically endarterectomy and stenting).

Methodology

Search Strategy

A MEDLINE and PubMed search with conducted of the following search terms: *cerebral vascular accident* and *stroke* and *cerebral infarction*. These topics were then further searched with the additional terms: *patent foramen ovale, atrial fibrillation, hypothermia, left atrial appendage, clot retrieval, MERCI, intra-arterial revascularization, stenting, and endarterectomy*. Review articles were used to refer back to original data collected in research trials as well as reference lists. A search of UpToDate and AccessMedicine was utilized for background information and to review more reference lists on the topics searched in MEDLINE and PubMed.

Inclusion Criteria

While searching, only expert opinion review articles and primary research articles were selected. Only articles published in English were searched on ischemic stroke. Current peer-reviewed articles were also used.

Results

Treatment

Hypothermia for neuroprotection.

Results from a 1996 study suggest that, increased body temperature had effects on the outcome of stroke such as the lesion size, stroke severity and the patient's final outcome (Reith et al., 1996). During the first days following ischemic stroke, hyperthermic states often develop due to infection, thrombophlebitis, or central causes related to infarct (Castillo, Davalos, Marrugat, & Noya, 1998; Reith et al., 1996). Regardless of care, hyperthermic patients have shown a significantly greater mortality rate compared to patients with normothermia. It was concluded that control of body temperature in the first 24 hours following stroke is vital for the brain's cellular integrity (Castillo et al.). For decades, the use of hypothermia for neuroprotection in patients suffering from traumatic brain injury and cardiac arrest has been studied (Marion et al., 1997; Williams & Spencer, 1958). Now researchers have been studying the use of this therapy in preventing the ongoing neurologic losses in the first hours following an acute ischemic stroke. The penumbra, which contains neurons at risk for apoptosis, remains viable following ischemia, but the length of survival is uncertain. If reperfusion is obtained, these cells may survive (Siesjo, 2008).

In several animal studies the use of mild hypothermia has decreased the negative outcome seen when damage begins to further spread into the penumbra (Ridenour, Warner, Todd, & McAllister, 1992). Hypothermia has shown a benefit in these models by reducing the release of excitotoxic neurotransmitters such as glutamate (Baker et al., 1995), decreasing oxidative stress (Guven et al., 2002), reducing edema and blood brain barrier disruption (Karibe, Zarow, Graham, & Weinstein, 1994; Kollmar et al., 2002), and reducing inflammation (Kawai,

Okauchi, Morisaki, & Nagao, 2000). Another avenue of protection is the reduction in metabolism created by reducing the brain's temperature. Hypothermia reduces the metabolic rate of oxygen and glucose therefore leaving the brains ATP supply preserved (Erecinska, Thoresen, & Silver, 2003). Since the penumbra remains viable for several hours following stroke, neuroprotection with hypothermia increases the benefits of reperfusion therapy. This is due to a longer therapeutic window for hypothermia initiation versus reperfusion therapy alone. In the first few hours following stroke, positron emission tomography has revealed that approximately 70% of the infract volume is due to sudden hypoperfusion in the core, while 18% makes up the penumbra and 12% accounts for areas that were initially well perfused (Heiss, Thiel, Grond, & Graf, 1999). In the first few minutes after ischemia onset, oxygen is decreased, energy is depleted, cell depolarization occurs, and ion homeostasis is disrupted. In the hours that follow, the ion disruption and depolarization continue to spread and excitotoxic events begin. By the time ischemic insult has aged days to weeks, inflammation and apoptosis of brain cells may develop and contribute to an increase in the final infarct size (Heiss et al.). Due to this timeline, the injury that may occur in the hours and days following acute ischemic insult is the main target for hypothermic therapy and other neuroprotective strategies. Though, the viable area that remains may be as small as 30% (Heiss et al.), there is still potential to limit the final infarct size.

When considering the use of the therapeutic hypothermia, certain parameters have been researched such as the optimal depth and duration of hypothermia and the rates of rewarming. In animal models following stroke, hypothermic states of 33°C, for a duration of 1-2 hours, reveals significantly better neurologic scores in these animals versus those maintained in normothermic states (Maier et al., 1998). There was also no significant improvement in recovery time for those treated at deeper hypothermic states of 30°C versus those with 33°C temperatures, and deeper

hypothermia led to more drastic physiologic fluctuations (Maier et al.). When the rewarming parameters were studied, the rate at which animals were returned to normothermic temperatures resulted in differing levels of neuroprotection. To preserve the neuroprotection seen following therapy, a slower rate of rewarming has shown to be superior to rapid rewarming. When using uncontrolled and rapid rewarming in animal studies, the ischemic brain has shown an increase in pressure and inflammation (Berger, Xia, Kohrmann, & Schwab, 2007). Studies have also reported a re-elevation of lactate and glutamate to levels significantly higher than pre-ischemic states as well as levels directly following hypothermic therapy in animals returned to normothermic temperatures rapidly over 30 minutes (Nakamura et al., 1999). The size of the infarct was also affected by the rate of rewarming showing that animals rapidly returned to normothermic temperatures resulted in larger infarct sizes versus those rewarmed slowly over several hours (Berger et al.). Though more benefit was seen by a smaller infarct size in those slowly returned to normal temperatures, those rapidly rewarmed still showed smaller infarct sizes than those not treated acutely with hypothermia (Berger et al.).

In considering when the time threshold for benefit of hypothermia is reached after ischemic insult, several experiments have been carried out. Though basic models of intra-ischemic hypothermia in cases of global and focal ischemia have shown significant neurologic benefit (Busto et al., 1987; Morikawa et al., 1992), this experimental setting is not as applicable to what is seen in clinical practice. More recently, animal models of focal cerebral ischemia have shown significant decreases in infarct volume after treatment with hypothermia shortly before reperfusion and continuing on after reperfusion has occurred (Kawai et al., 2000). This data is more applicable to a stroke patient than that of cases showing benefit of hypothermia shortly after initiation of ischemic symptom onset. Neuroprotective benefit has been seen as late

as 3 hours following transient middle cerebral artery occlusion (1 hour postreperfusion) and the benefit continued to be evident even days following the occlusion (Kollmar et al., 2002).

After these animal studies demonstrated the beneficial effects of hypothermia, trials were approved to begin on human subjects. The feasibility of decreasing the core body temperate to a moderate hypothermic state, 32 to 34°C, was demonstrated in human subjects, but the efficacy required further investigation (Schwab et al., 2001). Further studies investigated endovascular cooling techniques instead of the previous surface cooling to reach a core hypothermic state. External cooling techniques include methods such as cold pack application to the head, neck, torso and limbs (Bernard et al., 2002), forced cold air mattresses over the entire body (Hypothermia after Cardiac Arrest Study Group, 2002), heat exchange pads placed on the back, abdomen and thighs (Haugk et al., 2007; Ly et al., 2005), use of ice water and whole body alcohol rubs (Krieger et al., 2001), and cooling caps (Qiu et al., 2006). Surface cooling has been criticized for being slower, cumbersome, and requiring sedation and neuromuscular blocking agents to reduce shivering (De Georgia et al., 2004; Schwab et al., 2001). As much as 3 hours or longer may be needed to reduce the body temperature to the desired hypothermic state with surface cooling (De Georgia et al.; Krieger & Yenari, 2004). The increased shivering due to surface cooling could also be a drawback to the external cooling techniques (Mayer et al., 2004). The use of paralysis to control shivering related to surface cooling, requires the use of sedation and intubation and makes this method less attractive (Krieger & Yenari). Surface cooling has also shown to less effectively lower the brain's temperature to the target hypothermic state so other more invasive techniques may be necessary. The safety and feasibility of endovascular cooling was concluded in the 2004 COOL-AID trial of 40 patients with ischemic stroke presenting within 12 hours of symptom onset (De Georgia et al.). In endovascular cooling, a

catheter is inserted in a peripheral vein, most commonly the femoral vein, and centrally placed in the inferior vena cava. This closed loop catheter continuously allows cold saline solution to enter the flexible heat-exchange element and cool venous blood as it flows past the cooling element catheter without allowing saline into circulation or blood into the catheter. The catheter is attached to an external mobile temperature-regulating device with a water bath. Based on the patient's body temperature, the saline circulating through the closed-loop system is cooled to allow for the target body temperature to be maintained (Georgiadis, Schwarz, Kollmar, & Schwab, 2001; Guluma, Hemmen, Olsen, Rapp, & Lyden, 2006; Krieger). The intravascular cooling technique was then further perfected in the 2005 Intravascular Cooling in the Treatment of Stroke (ICTuS) trial of 18 patients within 12 hours of stroke symptoms onset. The ICTuS trial induced hypothermia in awake patients while using the synergistic effects of buspirone and meperidine to overcome the major side effect of the therapy, shivering. This allowed for the patients to remain conscious during the procedure which may allow for a safer intervention for the elderly (Lyden et al., 2005). When using therapeutic hypothermia, the core body temperature is recommended to be kept at 32 to 34 ° C and this can be monitored by a variety of probes, including vaginal, rectal, tympanic, bladder, esophageal, or by placing a catheter in the pulmonary artery (De Georgia et al.; Lyden et al.; Nolan, Morley, Hoek, & Hickey, 2003). Though this method has shown to be a promising therapeutic option, more clinical investigation is underway to provide more large-scale data on the efficacy in humans. This method of neuroprotection does not come without consequences. The most commonly reported adverse events include electrolyte disturbances, cardiac arrhythmias, DVT, infections and minor effects such as shivering (De Georgia et al.; Lyden et al.; Polderman, Peerdeman, & Girbes, 2001).

Though the efficacy of this therapy in stroke requires further investigation, efficacy in cardiac arrest patients has been demonstrated for years. Following cardiac arrest, it is a race against time to return blood flow to hypoxic organs, including the brain, but reperfusion may also cause chemical reactions to occur leading to increased ischemic injury (Nolan et al., 2003). Prior to revascularization, patients have been shown to benefit from therapeutic hypothermia (Oddo, Schaller, Feihl, Ribordy, & Liaudet, 2006). By using this therapeutic technique, patients resuscitated from out-of-hospital cardiac arrest due to ventricular fibrillation as well as those in shock show significant improvement in neurologic outcome compared to those treated with normothermic conditions (Hypothermia after Cardiac Arrest Study Group, 2002; Oddo et al.). There has been enough data on the efficacy of therapeutic hypothermia to allow for the Advanced Life Support (ALS) Task Force to recommend its use in certain situations of cardiac arrest (Nolan et al.).

Intra-arterial (IA) thrombolysis.

With the many limitations on use of intravenous (IV) t-PA, delivery of IA thrombolytics may be an option to increase the number of persons eligible for thrombolytic therapy. In a population-based study only 22% of ischemic stroke patients presented to the emergency department within the 3 hour window for IV t-PA administration and of the those 22% only 49% were eligible for IV t-PA administration (Kleindorfer et al., 2004). Eligibility for t-PA is discussed in Table 1. Non-time related exclusions included low NIH Stroke Scale score (indicating minor deficit), severe hypertension, elevated prothrombin time, decreased platelet or glucose levels, or specific past medical and surgical histories. Even when time was not an excluding factor, only 29% of all patients in this study were eligible for IV t-PA (Kleindorfer et

al., 2004). Efficacy of t-PA is based on rapid and complete recanalization as well as on neurologic outcome of patients following treatment (Rha & Saver, 2007; "Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group," 1995).When considering the rate of recanalization using intravenous administration of thrombolytics, the rate of large arterial recanalization with IV t-PA is as low as 12.5% for the internal carotids and proximal middle cerebral arteries and 27.3% for the distal middle cerebral artery occlusions (Lee et al., 2007). For those who suffer from large artery occlusion, other options are necessary.

According to the Guidelines for the Early Management of Adults with Ischemic Stroke (Adams et al., 2007), intra-arterial thromboylsis is an indicated treatment in certain situations. It can be considered in patients that present with major stroke within 6 hours of symptom onset due to an occlusion of the middle cerebral artery (MCA) who are not candidates for IV t-PA. This therapy should be given only in an experienced stroke center that has the proper equipment and trained staff. The treatment may be of benefit in other patients who are not candidates for IV t-PA (Adams et al.), as discussed in the following paragraphs. According to the American College of Chest Physicians Evidence Based Clinical Practice Guidelines, as mentioned previously certain criteria must be met for a patient to qualify for IV t-PA administration. Table 1 provides the inclusion and exclusion criteria (Albers, Amarenco, Easton, Sacco, & Teal, 2008; "Tissue plasminogen activator for acute ischemic stroke," 1995).

There have been many trials that have studied the feasibility and safety of intra-arterial therapy. In the Emergency Management of Stroke (EMS) Bridging trial, a combined intravenous and intra-arterial approach was compared to intra-arterial therapy alone. The procedure was found to be safe and an increased recanalization rate was seen with the combined approach, but a

better neurologic outcome was not seen in the combined treatment population (Lewandowski et al., 1999). After the initial two hours of the combined therapy, there was a recanalization rate of 54%, compared to 10% in those receiving only IA therapy. The rate of symptomatic ICH was comparable to that of the NINDS trial of IV t-PA and the rate of hemorrhage between the experimental and control group revealed no significant difference. Though the combined approach appeared superior by recanalization rates, the mortality in the patients who received the IV/IA therapy was higher than IA alone with 5 deaths in the occurring in those with combined approach compared to only 1 death in the IA group, but this was not found to be a statistically significant difference (P=0.06). Several adverse events that caused an increase in mortality in the combined study population could not be directly contributed to the treatment (Lewandowski et al.).

In the PROACT I clinical trial, the efficacy and safety of recombinant prourokinase was demonstrated in acute ischemic stroke caused by occlusion of the middle cerebral artery. Recombinant prourokinase (rpro-UK) was found to have greater recanalization when compared with placebo results and an even greater rate when combined with heparin (del Zoppo et al., 1998). Though the recanalization rate was increased, the rate of hemorrhagic transformation also increased with the dosage of heparin given (del Zoppo et al.). Investigators now sought to look at the effects of dosage of r-proUK on the recanalization rates. In the PROACT II study, the rpro-UK was increased and assessment of recovery was based on degree of neurologic disability after the treatment, and degree of recanalization of the middle cerebral artery was measured. The recanalization rate increased with the increased dose of rpro-UK along with the rate of symptomatic brain hemorrhage compared to PROACT I patients. Though the hemorrhage rate was increased, the baseline median NIHSS scores in these patients was much higher than those

in PROACT I (A. Furlan et al., 1999). Along with the risk of ICH, the time elapsing from arrival at the hospital and delivery of the agent was of concern (A. Furlan et al.). Due to the consideration of the time it took for initiation of IA therapy, researchers began the Interventional Management of Stroke Study (IMS).

The IMS study concluded that effective treatment of acute ischemic stroke can begin much sooner if a combined approach of IV/IA t-PA were adopted. Mortally at 3 months was reduced to 16% versus 24% seen in the NINDS trial, but rate of asymptomatic hemorrhage was increased. Symptomatic hemorrhage rate was comparable to NINDS rt-PA treatment rates (IMS Study Investigators, 2004). As in the PROACT II study, the patients also had a higher baseline NIHSS score, clot burden, and prevalence of vascular disease than those enrolled in the IV r-tPA NINDS study. Thirty-five percent of the participants had a major occlusion in the carotid which was many times accompanied by a thrombus of the MCA (IMS Study Investigators). Those with internal carotid artery (ICA) occlusion were much more likely to have hemorrhage with a rate as high as 71%, but only 42% of those with MCA or vertebral artery thrombus suffered from hemorrhage. When controlling for baseline NIHSS scores, age, and time in which treatment was given, persons receiving IV and IA therapy in the IMS trial showed a more improved outcome at 3 months than those treated with IV therapy in the NINDS trial. Since an interventionalist is not necessary for IV t-PA delivery, this treatment can be initiated as soon as ischemic stroke is diagnosed before transfer to a comprehensive stroke center for IA thrombolytic treatment. In this trial, the feasibility of the combined approach was demonstrated but a controlled trial is needed to compare the efficacy of this approach with the conventional IV t-PA used alone (IMS Study Investigators).

The ability to further dissolve a thrombus by adding ultrasound technology to the IA/IV combined method was investigated in the IMS II trial (IMS II Trial Investigators, 2007). By using a small-vessel ultrasound infusion system, the EKOS micro-infusion catheter, along with IV and IA thrombolytics, more arteries were found to have more complete reopening than in the IMS I trial (IMS II Trial Investigators). When comparing the rate of recanalization at a specific site of arterial occlusion, the rate of grade 2 and 3 recanalization rose from 56% in the IMS I trial to 73% in IMS II trial. The rate of symptomatic hemorrhage was not significantly different than that of the NINDS, but the patients with symptomatic hemorrhage had an average NIHSS score of ≥21 in IMS II. With age and baseline NIHSS score adjustment, the patients in IMS II showed a significantly better outcome at 3 months than in the NINDS rt-PA study, but the mortality rates were not significantly lower than in IMS I and the NINDS trial. The recanalization rate rose from 30.4% in the IMS I to 36.4% with the use of the EKOS catheter, but this was not found to be a statistically significant difference (P=0.9916). When compared to the PROACT II study, the mortality rate was lower, which was attributed to the faster initiation of therapy in the IMS II study (median 2 hours and 20 minutes versus 4.7 hours in PROACT II) (IMS II Trial Investigators). Diagnostic cerebral imaging was initiated at a median of 4.5 hours after stroke symptom onset in PROACT II (A. Furlan et al., 1999).

Several of the limitations or criticisms of the interventional therapy are elements such as time-to-treatment or door-to-drug, the cost, and the invasive nature of the procedure (Suarez et al., 1999). Some argue that not only the safety and efficacy of interventional treatments need to be considered. The quality of life that patients have following the treatment must also be weighed into the equation as well as the benefit seen for the cost of the intervention (Lewandowski et al., 1999). A condition for the use of intra-arterial thrombolytics, the occlusion

must be visualized to deliver the agent directly into the thrombus. This involves use of angiography and catheter insertion through a peripheral arterial access site (del Zoppo et al., 1998; IMS II Trial Investigators, 2007; IMS Study Investigators, 2004; Lewandowski et al., ; Suarez et al.). This more invasive procedure requires an experienced stroke center with the proper personnel to initiate the treatment (Adams et al., 2007). The need for specially trained personal and proper equipment also increases the cost of the procedure itself, but this might be offset by the improved neurologic benefit and decreased disability from stroke by utilizing the technique (Lewandowski et al.; Suarez et al.). Also of concern is the time needed to get the team in place for the procedure and to set up the equipment. In one study the average time to initiation of IA therapy was 130 minutes after stroke symptom onset, which is 70 minutes over the recommended hour to initiation of IV t-PA (Suarez et al.). Though the need for direct visualization of the thrombus creates a delay in thrombolytic administration, it allows for visualization of thrombi and a reduced amount of agent needed to lyse the thrombus. A study reported that the amount of agent used was reduced below the maximum level in 89% of patients which in turn decreases the risk for hemorrhage (Suarez et al.).

Recanalization rates are an indicator of the efficacy of thrombolyic therapy (Rha & Saver, 2007). In one meta-analysis, it was reported that recanalization for specific interventions was as follows: intravenous fibrinolytic (46.2%), intra-arterial fibrinolyic (63.2%), and combined IV/IA (67.5%) (Rha & Saver). The type of intervention also showed differing recanalization rates based on the specific arterial occlusion. In both the MCA and ICA occlusions, the IA and combined IV/IA therapies showed superior recanalization over IV thrombolytics (Rha & Saver). In a study of recanalization of the MCA, IA therapy led to lower mortality and higher occurrences of favorable outcome than IV. Mean time to initiation of IV thrombolytics after

onset of symptoms was 156 minutes while mean time to IA thrombolytic delivery initiation was over an hour later at 244 minutes (Mattle et al., 2008). When looking at the outcomes from IA recanalization, it was found that a patient's age (Jahan et al., 1999), lower NIHSS stroke score, time to recanalize, and degree of the infarct had a significant impact of the patient's final outcome (Ford, 2006; Gonner et al., 1998). The therapy has also shown to be more efficacious the earlier it is delivered (Gonner et al., 1998). When these factors are taken into account, IA therapy may be the best therapy for certain patient populations. The site of the occlusion also requires consideration of which therapy might be most efficacious, especially for MCA, ICA, and basilar artery occlusions (Ford; Mattle et al.; Rha & Saver). In patients that fail to reperfuse within 2 hours of IV thrombolytic therapy, administration of IA therapy may be the most appropriate next step (Ford). Certain factors also contribute to the risk of hemorrhage after IA thrombolytic therapy such as higher NIHSS score, comorbid atrial fibrillation, and the particular vessel occluded (IMS Study Investigators, 2006; Kidwell et al., 2002).

Though more investigation is needed to compare combined IV and IA approaches directly in a randomized controlled study with IV t-PA, this approach has been recommended for patients that are not candidates for conventional treatment, as mentioned earlier (Adams et al., 2007). Much anticipation awaits the results of the ongoing IMS III trial, which is investigating the comparison of IV/IA to standard IV t-PA therapy and also utilities technologies such as the EKOS infusion catheter and FDA-approved MERCI retriever (Khatri et al., 2008).

Clot Retrieval.

In previous studies, it has been shown that intravenous t-PA is not sufficient to lyse clot arising in large intracranial artery occlusions such as the MCA, ICA, and basilar arteries (Saqqur

et al., 2007). These types of occlusions need other interventions because these patients are faced with a higher mortality rate and poorer neurologic outcome (Smith et al., 2006). A novel idea was to use a device that would directly capture the thrombus and remove it from cerebral vasculature (Molina & Saver, 2005; Stead, Gilmore, Bellolio, Rabinstein, & Decker, 2008). With this idea, in 2004 the FDA approved a mechanical device to remove clots from the intracranial arteries of acute ischemic stroke patients. Since many remain ineligible for thrombolytic therapy, this is a potentially life-saving option. By using endovascular embolectomy, the time window for therapy is extended to up to 8 hours in large artery occlusions accessible by the retriever and successful revascularization was reported in 46% of patients (Smith et al., 2005). Intracranial vessel occlusions in this study included: vertebral, basilar, ICA, internal carotid bifurcation, or MCA. Recanalization was obtained in all major cerebral vessels where thrombolytics alone may be unable to effectively dissolve the clot. Though the mortality may be higher among patients treated with this method (44%) as compared to other interventions, this may be the only viable option in those with large artery occlusion (Smith et al.). The increased mortality rate in this study may also be attributed to the patient population which had a median age of 67(±15.5) years old and a mean baseline NIHSS of 20.1(±6.6). The stroke severities and site of occlusion may also have contributed to the high mortality rate (Smith et al.). Though the mortality rate is high, the rate of symptomatic intracranial hemorrhage was only 5% (Smith et al.), which is comparable to that of 6% in NINDS, 7.8% in IMS I (IMS Study Investigators, 2004) and 10% in PROACT II (A. Furlan et al., 1999).

In the MultiMERCI Trial that followed, researchers tested the use of clot retrieval in patients with large vessel occlusion who were treated with thrombolytics and failed to recanalize. A new retrieval device was also investigated. Recanalization was obtained in 57.3% of those

treated with the new generation retriever (L5 Retriever) verses the 45% recanalization with the old generation MERCI (X5 and X6 Retrievers). They also found that pretreatment with IV tPA did not increase the rate of intracranial hemorrhage as compared to those who received no thrombolytics and as a result concluded that the use of clot retrieval post-thrombolytics did not raise safety concern. They also discovered that when patients received IA therapies as an adjunct, the recanalization rate rose to 69.5% in those using the new generation L5 Retriever and 63.6% in those using the older generation retrievers. When comparing the retrievers, use of the new generation retriever was associated with lower mortality and higher rates of good outcome. Those who obtained revascularization post-retrieval had a 49% rate of favorable outcome versus 9.6% in those that did not recanalize. The mortality rate was 25% in the recanalized population versus 52% in those without revascularization (Smith et al., 2008).

Through these studies not only was clot retrieval found to be an option for those ineligible for thrombolytics or unable to benefit from IV tPA conventional treatment, it may also be used with other methods of revascularization to increase the recanalization rate in large vessel occlusion. Several new devices are currently in clinical trials, but the MERCI system remains the only FDA-approved device for clot retrieval (Molina & Saver, 2005).

Prevention

The Maze procedure and left atrial appendage procedures in atrial fibrillation.

Atrial fibrillation is the most common sustained arrhythmia and stroke is found to be one of the significant complications of this condition (Henry & Ad, 2008). This potentially fatal arrhythmia has proven to be an independent risk factor for stroke, increase the risk of stroke by as much as 5-fold (Wolf, Abbott, & Kannel, 1991). Even though anticoagulation is found to be

beneficial in lowering the risk for cardioembolic stroke in these patients, it does not eliminate the risk (Cox, Ad, & Palazzo, 1999), and not all persons are eligible for the therapy. For those in need of other options, several surgical procedures can be preformed to reduce or, in some cases, eliminate the risk for stroke in patients with atrial fibrillation. These procedures include techniques such as using cardiac incisions or radiofrequency ablation to reroute the abnormal pacing of the heart that occurs during fibrillation. The incision-based procedure, known as the Maze procedure, involves suturing of ablated lesions in the atria in an attempt to interrupt the reentrant circuits that occur during atrial fibrillation (Henry & Ad, 2008).

Over the years, this procedure has undergone many modifications, such as the exact placement of incisions, in an attempt to make the procedure easier to perform (Henry & Ad, 2008). After many modifications, this procedure is now widely known as the Maze III. After receiving the Maze III procedure, 98.2% of patients were cured of their fibrillation. This resulted in an overall stroke rate of only 0.7% in the perioperative period and only 0.4% over the next 11.5 years following the procedure. TIA rate was 0.7% in the perioperative period and 0.8% over the following 11.5 years (Cox et al., 1999). The stroke rate is as high at 4.5% in control patients not receiving ablation therapy ("Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials," 1994). The Maze procedure not only restores sinus rhythm, but the left atrial appendage is also either excised or the orifice is surgically closed during the operation. Since this orifice is an open structure in virtually all patients, stasis of blood in the appendage during fibrillation results in the perfect mixture for thrombus formation (Cox et al., 1999).

Though the Maze III procedure is effective, additional advances in procedural techniques have been made in an attempt to maximize time and energy spent during atrial fibrillation

augmentation. The Maze is now being replaced by new modified procedures that use energy sources for ablation such as radiofrequency, cryothermy and microwave energy. The new procedures prove to be less extensive and technically simpler (Chiappini et al., 2004; Henry & Ad, 2008). A procedure known as the Maze IV, uses the same method as in the Maze III, but utilizes the energy source technology. In a clinical setting that compared the Maze IV that used radiofrequency and cryoablation to the incision-based Maze III, the newer procedure required less time and skill (Lall et al., 2007). Though it was said to be simpler, the clinical outcome was not significantly different between the procedures (Lall et al.; Sie et al., 2001). The mean time of hospital stay, need for a permanent pacemaker, and freedom from atrial fibrillation were similar between groups, but the cross-clamp time was 121 ± 34 for the Maze III and 76 ± 37 minutes for the Maze IV (Lall et al.). The ablation time versus incision time was said to differ between the two procedures requiring approximately 12 minutes for ablation and 19 minutes for the incisions in Maze III (Cui et al., 2008). At final follow-up in patients treated with radiofrequency ablation, 89% of patients were still on Coumadin up to 26 months post-operatively (Cui et al.).

A newer addition to atrial fibrillation preventive therapy is the use of magnetic guidance ablation. By using a catheter place in the heart from a peripheral access site, a magnetic field is created by electromagnets placed around a patient's torso to allow for guided movements of the catheter tip in any direction in 3D space (Faddis et al., 2002; Katsiyiannis et al., 2008). The catheter is deflected in any direction by a computer that generates a magnetic field. This allows for more precise control of the catheter in difficult ablation procedures. When tested against the conventional ablation procedure, the catheter did not prove to have superior success at reaching predetermined cardiac sites, but researchers say that its precise movements and flexibility make

the technique of interest for the future (Faddis et al.). It has also shown safety and efficacy in human trials (Faddis et al., 2003).

Another approach that has been investigated for atrial fibrillation treatment is known as the radial approach. This procedure is much like the Maze, but incisions are made in a much different pattern than in the Maze procedure. Incisions are designed to allow for the function of the atria post-operatively to be comparable to that of a normally functioning atria. In this procedure, the incisions radiate form the sinus node toward the atrioventricular annular margins. This is said to allow for atria to optimize ventricular filling while the maze procedure leads to a longer activation time of the atria (Nitta, Lee, Schuessler, Boineau, & Cox, 1999). Activation time of the left atria was 53.6 milliseconds with the radial procedure versus 70.5 milliseconds with the Maze procedure, but no significant difference was senn in the right atria activation time between the procedures (Nitta, Lee, Watanabe et al., 1999). The right atrial appendage is also not excised in this procedure due to the concern of augmentation of atrial natriuretic peptide levels (Nitta, Lee, Schuessler et al.). When compared, the Maze and radial approaches equally prevented atrial fibrillation, but the rhythm was more synchronous and the procedure was technically easier with the radial method (Nitta, Lee, Watanabe et al.).

Though the Maze procedure and radial approach both equally cured atrial fibrillation in the majority of patients, the radial approach provided a greater left atrial transport function. Atrial transport function was determined by the peak atrial filling (A)/early filling velocities (E) as well as the atrial filling fraction (AFF). The left peak A/E was significantly larger following the radial procedure at 0.58 compared to an A/E of 0.25 for the incision procedure while the left AFF was 43% following the radial approach versus 33% following the maze. The right atrial function was not found to be significantly different between the two techniques. These values

were determined by transthroacic Doppler echocardiography at 3±1.6 months following the radial procedure and not until 42.9 ± 12.0 months following the maze (Nitta, Ishii et al., 1999). The radiofrequency technology as compared with Maze III incisions appear to show relatively equal clinical outcomes, but in an effort to allow for more efficient operating room time, energy ablation may eventually replace the incision based methods. As time goes on, more modifications to these current treatments will undoubtedly occur as well as the development of new techniques.

Another area with potential for decreasing the risk of thromboemolism in patients suffering from atrial fibrillation is ligation or occlusion of the left atrial appendage (LAA). In patients with non-rheumatic-related atrial fibrillation, thrombi were found to be localized to the appendage in 91% of cases and 57% of cases in those with rheumatic atrial fibrillation. Transesophageal echocardiogram (TEE) studies also revealed that in cases of atrial thrombi, as many as 98% of those were found in the LAA (Blackshear & Odell, 1996). Several studies have looked at the effects of excluding the appendage at the time of other cardiac surgeries, such as valvular repair and the Maze procedures (Garcia-Fernandez et al., 2003; Katz et al., 2000). Other techniques include isolated procedures for appendage obliteration or occlusion with implantable devices. Some of these procedures may even be done less invasively with percutaneous transcatheter techniques (Fountain et al., 2006; Ostermayer et al., 2005).

Though the ACC/AHA guidelines for the management of valvular heart disease recommend the ligation of the appendage during valvular procedures to reduce the future risk of thromboembolism (Bonow et al., 2008), there is still concern about risks of ligation and occlusion. The major concern of ligation techniques is incomplete ligation. During valvular surgery, incomplete ligation was found in several different instances with a rate as high as 36%

of patients (Garcia-Fernandez et al., 2003; Katz et al., 2000). These studies also found that these incomplete procedures still allowed for increased risk of thromboembolism compared to patients who had successful complete ligation (Garcia-Fernandez et al.; Katz et al.). When considering patients undergoing mitral valve replacement, the risk of cardiac embolism was reduced 12-fold in those with complete left atrial appendage ligation compared to those without ligation (Garcia-Fernandez et al.). It was also concluded that risk is associated with procedural technique (i.e. suturing) and not in post-operative degenerative processes (Katz et al.). Along with procedure error, some are concerned that complete obliteration of the appendage may lead to a disruption in cardiac function. This disruption of function may arise due to physiological roles of the left atrial appendage such as its relationship to pressure and volume as well at its release of atrial natriuretic peptides (Hoit et al., 1993; Inoue, Murakami, Sano, Katoh, & Shimada, 2000; Rodeheffer et al., 1993).

These concerns are what led to the interest in other options for LAA exclusion such as occlusion. Several occlusive devices have been studied both through surgical and percutaneous delivery. Two of the percutaneous devices are the PLAATO and WATCHMAN systems. Both are self-expanding cages with nitinol frames with varying materials covering the frames (Fountain et al., 2006; Ostermayer et al., 2005). The devices also come in varying dimensions to accommodate the various sizes of appendages. These procedures require only general or local anesthesia and allow for faster recovery than with surgery due to the less invasive technology (Ostermayer et al.). The PLAATO reported an annual stroke rate of 2.2% in patients following appendage occlusion. Since this population of patients had an estimated annual stroke risk of 6.3% if taking aspirin, the procedure resulted in a 65% relative stroke reduction. At 6 month follow-up, 87% of devices had trace or no leaks present, while 13% revealed only mild leaks. In

the strokes that did occur, the devices showed trace or no leaks before and after the event and showed no sign of thrombus formation on the device itself (Ostermayer et al.). Due to unknown reasons, the manufacturers of the PLAATO devices have discontinued development of the product. The WATCHMAN device showed similar success to the PLAATO with 91.7% of patients discontinuing Coumadin (warfarin) usage 6 months following implantation (Sick et al., 2007). At one year follow up, no strokes had occurred (Sick et al.). There were several patients who experienced TIAs and several patients formed thrombi on the surface of the device (Sick et al.). The findings of the ongoing randomized trial comparing the WATCHMAN and anticoagulation therapy are much anticipated to allow for a more thorough look at the safety and efficacy of the procedure (Fountain et al., 2006).

Though to date the device implantation procedures seem relatively safe, complications such as device failure, dislodgement, cardiac injury, and incomplete occlusions are of concern (Ostermayer et al., 2005; Sick et al., 2007). The WATCHMAN showed successful implantation in 93% of cases, but device failure occurred in 3 out of 16 patients treated with the first generation device, 2 resulting in device embolization. Once being redesigned as a result of the device failures with the first-generation WATCHMAN, no device embolization occurred with the second-generation device. One case of pericardial effusion occurred in each device group (i.e. first and second generation devices) out of a total 75 procedures (Sick et al., 2007). As mentioned before, mild leaks were found in several cases in the PLAATO devices, but they were not concurrent with stroke incidence (Ostermayer et al., 2005).

Atrial Septal Defect Closure Devices.

Cryptogenic stroke, or stroke without determined cause, has been found in as many as 40% in those younger than 55 years (Sacco et al., 1989). This has led researcher to believe that a cardiac abnormality known as patent foramen ovale (PFO) may be the source of stroke in younger patients. PFO is a common condition with a prevalence of approximately 20%-27% in individuals younger than 50 years of age and is thought to be the most common cause of stroke in this age group (A. J. Furlan, 2007; Hagen, Scholz, & Edwards, 1984; Meissner et al., 1999), although there remains some debate on this issue (Petty et al., 2006). Patent foramen ovale is a congenital birth defect caused by the incomplete closure of the foramen ovale that is present in all humans in utero. Normally after birth, physiologic lung and cardiac development cause cardiac pressure changes therefore closing the ovale against the atrial septum (Jaquis, 2007). There exists a possibility for right-to-left shunting if the foramen ovale does not close and the pressure in the right atrium exceeds the left, causing paradoxical embolism, which could lead to an ischemic cerebral event. An embolism may arise from the passage of a systemic venous thrombus through the septal defect. This mechanism, as well as possible thrombi originating from the atria, is thought to be a possible cause of stroke in some patients with PFO (Hausmann, Mugge, & Daniel, 1995; Overell, Bone, & Lees, 2000).

There is speculation that anatomical variations may increase risk of stroke in patients with PFO. Studies suggest that a PFO coexisting with atrial septal aneurysm (ASA) is a greater risk factor for cryptogenic stroke than lone PFO (Force, Massabuau, & Larrue, 2008; Mas et al., 2001). A 2001 study covering the use of aspirin therapy to prevent recurrent stroke in patients with PFO found that after four years the rate of recurrent stroke in individuals with PFO alone was 2.3 percent compared to 15.2 percent in patients with both PFO and ASA (Mas et al.). The increased rate of recurrence in patients with both anomalies suggests that therapy other than

antiplatelet medication may be necessary (Mas et al.). In another study of patients with PFO, the presence of coexisting PFO and ASA was found in 45% of patients who had experienced either a stroke or TIA versus 21% in those with asymptomatic PFO (Goel et al., 2009). Having both cardiac anomalies has shown to increase a person's odds of having a stroke by 33 times that of a person possessing no defects (Cabanes et al., 1993). Patients with an aneurysm with >10mm excursion have also shown to have a greatly increased risk of an ischemic event compared to patients with smaller excursion (Cabanes et al.). Some researchers believe that part of the increased risk of stroke in those with these cardiac anomalies may be due to a transient or paroxysmal atrial fibrillation that may occur due to the abnormal cardiac anatomy (Berthet et al., 2000). This possible occurrence of arrhythmia therefore puts the patient at a greater risk for thrombi formation (Berthet et al.).

Not only do co-morbid cardiac anomalies appear to put the patient with PFO at an increased risk for an ischemic event, but also the anatomy of the PFO itself. The size and degree of shunting through the cardiac defect has also been studied. An increased size of the PFO, or the length of separation between the septum primum and septum secundum, has shown to be more frequently associated with stroke rather than smaller separation. In a 2009 study, patients who had experienced either TIA or stroke had PFOs with an average of 3.9 mm as compared to those that were asymptomatic who had an average of 2.9 mm PFO (Goel et al., 2009). In this same study, the degree of right-to-left shunting and PFO tunnel length also differed between groups. Symptomatic patients were found to have more severe degrees of shunting and longer PFO tunnels (Goel et al.)). The Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) also found larger PFOs to be more frequent among those with cryptogenic stroke (20.0%) compared to those with known stroke cause (9.7%) (Homma, Sacco, Di Tullio, Sciacca, & Mohr, 2002).

Whether age influences the potential risk for stroke recurrence in persons with PFO, thus creating the need for more aggressive therapy, is another highly debated issue. Studies have shown an increased prevalence of PFO in individuals with cryptogenic stroke in both younger (<55 years of age) and older (≥55 years of age) populations than in individuals who have had a stroke due to a known cause (Handke, Harloff, Olschewski, Hetzel, & Geibel, 2007). In another study of stroke/TIA, with patients ages 55 years and older, PFO and ASA were more prevalent in cryptogenic cases (19%), than in those with a known cause of stroke/TIA (3%), and this remained significant when adjusted for age (Force et al., 2008). Though PFO appears to be more prevalent in patients who suffer TIA or stroke at<55 years of age, other pathological cardiac abnormalities increase in those whose age is >55 years (Knebel et al., 2009). One study reviewing the prevalence of PFO in different patient populations also points out that there may be a bimodal peak resulting in another increase in prevalence in individuals >79 years old (Gupta et al., 2008). PFO size has also been shown to increase with age which may put those ≥55 years at an increased risk for a paradoxical embolism (Di Tullio, Sacco, Gopal, Mohr, & Homma, 1992; Hagen et al., 1984). While some studies point to PFO and ASA as a risk factor for stroke in those ≥55 years, there is limited data on this population and some researchers believe that other stroke risk factors are more likely to be causative (Overell et al., 2000). Other researchers believe that management should not differ based on patient age (Force et al.).

Healthcare providers have several options for stroke prevention in patients that have recurrent cryptogenic stroke with an associated PFO. Possible prevention techniques include closure of the foramen by surgical means or by percutaneous occlusion of the foramen as well as medical treatment with anticoagulants or antiplatelets (Homma et al., 2002). The 2002 PICSS demonstrated that medical treatment in those with and without PFO showed no significant

difference in recurrent stroke or death rate. In addition, the rates were not significantly different when comparing warfarin treated patients to those treated with aspirin (Homma et al.). Though rates of recurrent stroke were similar in this instance, closure of the PFO may be necessary if the patient continues to be symptomatic while receiving medical therapy or has contraindications to antiplatelet or anticoagulant therapy (Homma et al.). Also in a retrospective study of the results of PICSS, researchers found that patients ≥65 years old, were indeed at a greater risk for recurrent event when treated medically with aspirin and warfarin then those <65 years old, even when the prevalence of large PFOs was higher in the young study population (Homma, DiTullio, Sacco, Sciacca, & Mohr, 2004).

In addition to medical therapy, there are currently several devices being used in clinical trials for percutaneous and surgical closure of PFO. In a study of the long-term results of 152 patients with PFO and presumed paradoxical embolism who received a device, the implantation success rate was 99% and complete closure, or no remaining shunt, was achieved in 79% of patients. In the first year following device placement, 95.1% of patients had no signs of paradoxical embolism and 90.6% still remained embolism free at 6 years post-placement (Wahl et al., 2001). A remaining residual shunt through the PFO may have been a contributing factor to some of the paradoxical embolism recurrence reflected by a 98.1% rate of freedom from recurrent embolism at 1 year in those with no residual shunting after closure (Wahl et al.). This study also revealed low morbidity and no mortality using device closure and the use of newer devices specific for PFO closure led to the best results and fewest complications (Wahl et al.). Newer devices such as the Amplatzer PFO occlude have shown a 0% recurrence rate of embolism at follow-up in addition to low complication rates of 2% or below (Slavin et al., 2007; Thanopoulos, Dardas, Karanasios, & Mezilis, 2006). Other PFO closure trials show similar

major complication rates of approximately 1.5% (Khairy, O'Donnell, & Landzberg, 2003). Possible complications include death, hemorrhage, pulmonary embolism, arrhythmias, air embolism, dislodgement and embolization of device parts, cardiac tamponade, and puncture site injury (Khairy et al.; Wahl et al.). In a systemic review of 16 studies including 2250 patients, medical therapy was compared to PFO closure. In the first year with medical management, recurrence of stroke or TIA rate ranged from 3.8% to 12.0% while device closure led to recurrence rates much lower (0% to 4.9% at 1 year follow-up) (Khairy et al.). When reviewing this data, one must also take into consideration that the medically treated patients had more stroke risk factors such as smoking, hypertension and diabetes (Khairy et al.).

To further determine if closure of the foramen is beneficial over medical therapy, one must examine the results from the ongoing trials testing this hypothesis. Several of those trials include: Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial, Evaluation of the STARFlex Septal Closure System in Patients with a Stroke or TIA due to Possible Passage of a Clot of Unknown Origin through a Patent Foramen Ovale (CLOSURE-1), and PC (Percutaneous Closure)-trial: Patent Foramen Ovale and Cryptogenic Embolism (Handke et al., 2007). Many are anticipating the completion of these trials, but closures being performed outside of these studies may be slowing the enrollment, the results, and in the end, device FDA approval (Kaplan, Lukovits, & Robb, 2007).

Endarterectomy and Stenting for Carotid Stenosis.

Carotid endarterectomy (CEA) and other operations such as angioplasty and stenting do not have enough data on their safety and efficacy in the acute ischemic stroke patient to

recommend that there be procedures for treating patients in this setting. The risks of endarterectomy may outweigh the benefits due to rapid restoration of blood flow causing an increased risk of developing brain edema or hemorrhage during an acute attack. Emergency angioplasty also has not achieved a role in acute treatment, but eventually may (Adams et al., 2007). Though these interventional techniques may not be currently recommended for emergency treatment in acute ischemic stroke, they may play a role in prevention of stroke and recurrent stroke in patients with carotid arterial disease.

Today several treatment options are available for patients with carotid atherosclerosis which include: medical management (antihypertensives, lipid-lowering agents, and antiplatelet agents), surgery (endarterectomy), and newly available angioplasty and stenting (Adams et al., 2007; European Carotid Surgery Trialists' Collaborative Group, 1998). Patients with large artery stenosis of greater than 50% show a rate of ischemic stroke of approximately 17% as of 2003 data (Carrera, Maeder-Ingvar, Rossetti, Devuyst, & Bogousslavsky, 2007). According to the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) investigators, carotid atherosclerosis is to blame for 20% of all ischemic and transient ischemic attacks in patients with symptomatic severe carotid stenosis. Even with medical treatment, recurrence remains alarmingly high (CAVATAS Investigators, 2001).

Since medical treatment may not be of enough benefit for patients with higher degrees of stenosis, other options are available. At the current time, endarterectomy has shown to be beneficial in patients with symptomatic carotid disease with stenosis of greater than 50% and for asymptomatic disease with stenosis of greater than 60% (Barnett et al., 1998; Mohammed & Anand, 2005). The North American Symptomatic Carotid Endarterecmy Trial (NASCET) and European Carotid Surgery Trial (ECST) found similar rates in stroke and death in patients

receiving the surgical procedure. In NASCET, the total stroke and death rate at 90 days was 6.5% (Ferguson et al., 1999) and in ECST the overall rate of all major stroke and death was 7.0% (European Carotid Surgery Trialists' Collaborative Group, 1998). Endarterectomy was found to be effective in preventing recurrence ipsilateral stroke and was determined to be safe (Ferguson et al.). The ECST also showed that if the patient carries a significantly high chance of stroke due to a highly stenosed vessel, the surgery will greatly lower the risk of an event. The patient's odds of survival must be considered when deciding whether or not to perform the operation because even though the risks that it carries are small they are serious, either stroke or death. With extreme degrees of stenosis, this operation may be the only hope for the patient therefore outweighing the risk (European Carotid Surgery Trialists' Collaborative Group).

Overall, patients with carotid symptomatic stenosis of 70% or more benefit substantially from endarterectomy and those with moderate stenosis of 50 to 69% appear to benefit less. Therefore, when evaluating patients with less than 70% stenosis, risk factors must be closely considered. For those with less than 50% stenosis, surgery offered no benefit (Barnett et al., 1998). According to guidelines set forth by the American Heart Association/American Stroke Association Council, CEA is recommended in certain patients. For those with recent stroke or TIA in the past 6 months and ipsilateral severe carotid stenosis of 70% to 99% stenosis, CEA is recommended to be performed by a surgeon with perioperative morbidity and mortality of <6%. For those with moderate stenosis (50% to 69%), CEA is recommended depending on factors such as patient age, gender, co-morbidities, and severity of initial symptoms. According to these guidelines, those with <50% stenosis, CEA is not indicated (Sacco et al., 2006). All in all, the degree of carotid stenosis is the main determinant for what the benefit of endarterectomy may be and whether the procedure is recommended, but other factors such as the time in which the

procedure is performed following the first sign of symptoms has also shown to be important for its effectiveness (Rothwell, Eliasziw, Gutnikov, Warlow, & Barnett, 2004a). Patient data from NASCET and ECST showed that the benefit achieved from CEA decreased as time lapsed from last symptom onset and trial randomization time in those with 50% to 69% as well as those with ≥70% stenosis (Rothwell, Eliasziw, Gutnikov, Warlow, & Barnett, 2004b). For those randomized to the surgical trials within 2 weeks, the 5-year absolute risk reduction of ipsilateral stroke or TIA was approximately 30% and this risk reduction decreased as time progressed between last symptomatic event and surgery randomization (Rothwell et al.).

While surgery has found to be of significant benefit in patients with symptomatic carotid stenosis, those with stenosis that remain asymptomatic have not shown to benefit to the same degree. Several randomized trials have studied the benefits to CEA in asymptomatic carotid disease. The Asymptomatic Carotid Artery Stenosis (ACAS) study, which enrolled 1662 patient with ≥60% stenosis, estimated that the 5-year risk of ipsilateral stroke and perioperative stroke or death was 11% for the those treated with only aspirin and 5.1% for those treated with CEA. In a surgical group of 544 men and 281 women, the 5-year event rate was reduced 66% in men and 17% in women following CEA, although this difference is not statistically significant. Though the surgical group showed greater risk reduction (relative risk reduction of 53%) as compared to those treated medically, the study determined that 19 procedures would be needed to prevent 1 stroke over 5 years ("Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study," 1995). Another multicenter trial studying 444 males in 11 Veterans Affairs medical centers studied the benefit of surgery for asymptomatic atherosclerosis with ≥50 % carotid stenosis. With the mean follow-up of 47.9 months, the absolute risk reduction in all neurologic events (ipsilateral and contralateral transient

ischemic attack, transient monocular blindness, and stroke) was 11.6 % in those receiving CEA compared to those treated medically with aspirin. The absolute risk reduction in ipsilateral events was 12.6%. When considering the difference in incidence of stroke alone, there was no significant difference in risk reduction between treatment groups due to the perioperative deaths and strokes associated with arteriography in the surgical group (Hobson et al., 1993). In the international Asymptomatic Carotid Surgery Trial (ACST), a multicenter, randomized trial of 3120 patients, researchers compared outcome in patients with ≥60% asymptomatic carotid stenosis who immediately received CEA to those who deferred surgery over time. Those who received CEA showed a rate of any stroke over 5 years along with perioperative death at 6.4% compared to 11.8% in those in the deferral group. Initially though, the stroke rate was higher in the surgical group due to surgical hazards causing the benefit of CEA to be seen more significantly at 5 years following operation. Accounting for surgical hazards and the later benefits, CEA still led to a highly significant reduction in 5-year stroke and perioperative death rate (Halliday et al., 2004). Based on a systemic review of the three trials, the relative risk reduction of perioperative stroke or death or subsequent ipsilateral stroke was 29% following CEA. When considering the benefit seen in men compared to women, a relative risk reduction of 51% in men versus 4% in women was shown following CEA. The study found that among the three trials the absolute risk reduction was only 3% over three years, meaning that for every 33.33 undergoing CEA one event will be prevented in 3 years (Chambers & Donnan, 2005).

Though patients with asymptomatic disease tend to show reduction in stroke risk with surgery, one must consider the number of patients needed to treat to prevent an event. According to guidelines created by the American Heart Association, for asymptomatic carotid stenosis of

>60% and the perioperative risk being <3% and the patient's life expectancy ≥5 years, then ipsilateral surgical treatment is acceptable (Biller et al., 1998).

Whereas endarterectomy is accepted for higher degrees of carotid stenosis in symptomatic and asymptomatic disease, the benefits of stenting remain highly debated. In 2001, The Carotid and Vertebral Artery Transluminal Angioplasy Study (CAVATAS) investigated the use of angioplasty and stenting over endarterectomy. They believed that angioplasty and stenting techniques may be promising due to the fact that the procedure is less invasive requiring only local anesthesia at the site of catheter insertion in the groin. Most of the patients in the trial were at very high risk for stroke with an average stenosis of the carotids being 86%. The researchers found the risk of stroke or death at 30 days following endovascular treatment to be similar among those treated surgically. There also was no significant differences in risk between the two procedures (CAVATAS Investigators, 2001).

Later in 2004, the Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy trial (SAPPHIRE) further supported the CAVATAS data by concluding that patients who received stenting had similar rates of stroke, death and myocardial infarction as those who received endarterectomy in a population at risk for surgery (Yadav et al., 2004). The data was also equivalent to the 2003 data from the Carotid Revascularization With Endarterectomy and Stenting Systems (CARESS) data that found no significant difference in death, stroke or myocardial infarction between patients treated with surgery versus stenting in patients that had >50% symptomatic stenosis and >75% asymptomatic stenosis (CaRESS Steering Committee, 2005). Recently, stenting has shown to be less promising. The Endarterectomy Versus Stenting in Patients With Symptomatic Severe Carotid Stenosis study (EVA-3S) was halted due to negative outcomes. The 30 day rate of stroke or death with

endarterectomy was 3.9% while for stenting it was 9.6%. The rates of stroke or death at 6 months were also lower after endarterectomy. In conclusion, symptomatic patients with greater than 60% stenosis had significantly better outcomes following endarterectomy (Mas et al., 2006). The Stent-Protected Angioplasty Versus Carotid Endarterectomy (SPACE) trial demonstrated that stenting was not inferior to surgery with more favorable results occurring in those treated with endarterectomy (Ringleb et al., 2006). Data from the ongoing Carotid Revascularization Endarterectomy Versus Stenting trial (CREST) and the International Carotid Stenting Study (ICSS /CAVATAS II) are much anticipated as these two trials have a combined total of approximately 3,000 patients, approximately double the number enrolled in the current randomized trials (Wiesmann, Schopf, Jansen, & Bruckmann, 2008).

Another factor to be considered in comparing surgery to stenting is cost. Some argue that even though the number of hospital days required for endarterectomy is slightly greater than for stenting, the cost is significantly greater for stenting when all costs are considered. The main costs of stenting are due to the stents themselves and other procedural devices used during the intervention (Janssen et al., 2008). Other studies have found similar results concluding that due to the high cost of supplies and inferior outcomes due to high stroke rates with CAS, CEA tends to be more cost effective (Jordan, Roye, Fisher, Redden, & McDowell, 1998; Kilaru et al., 2003; Pawaskar, Satiani, Balkrishnan, & Starr, 2007).

Another surfacing concern is the rate of restenosis in those treated with stenting due to the fact that the plaque is not removed; it is only pushed aside. A recent study found a significantly higher rate of restenosis in stented patients (6 of 32 patients) versus patients who underwent endarterectomy (0 of 29 patients) (Steinbauer et al., 2008). Another study reported a rate of severe restenosis (≥80%) at 8.7% (Chakhtoura et al., 2001). A recent meta-analysis of 8

randomized trials comparing stenting to surgery showed that stenting was associated with an increased risk of stroke or death in the first month following the operation (Wiesmann et al., 2008). The study did not, however, find a difference in the rate of disabling stroke or death between the two procedures (Wiesmann et al.). Surgery did result in higher rates of facial nerve palsy and myocardial infarction within 30 days following CEA compared to stenting (Wiesmann et al.). As the techniques of endovascular stenting improve over time, with standardized protocol for use of specific devices, such as closed verses open cell stents, and endovascular protection devices, benefits of stenting may become comparable to surgery (Wiesmann et al.). Though both surgery and stenting are options for the prevention of stroke in patients with carotid atherosclerotic disease, one must take into consideration the pros and cons of each treatment and the current data available on their effectiveness and long-term outcomes.

Conclusions

This review has presented several up-and-coming interventional modalities for the treatment of ischemic stroke, including hypothermia therapy, IA thrombolytics and clot retrieval. Hypothermia therapy shows great promise for the future care in decreasing the ongoing damage that occurs to the brain following acute ischemia (Ridenour et al., 1992). Though the use of hypothermia therapy in animal models subjected to ischemic events has shown benefit from the therapy, more research is needed in human models for the therapy to be recommended in the current standard of care for acute ischemic stroke (Ridenour et al.). Currently the therapy is recommended for use in certain situations of cardiac arrest to improve neurologic outcome in these patients (Nolan et al., 2003; Oddo et al., 2006).

As for treatments with IA thrombolytics and the clot retrieval, research has been able to bring about approval for these interventions in certain situations. According to the Guidelines for the Early Management of Adults with Ischemic Stroke (Adams et al., 2007), intra-arterial thromboylsis can be considered in patients ineligible for IV t-PA that present with stroke within 6 hours of symptom onset following middle cerebral artery (MCA) occlusion. One must also take into consideration the requirement that the therapy is given in an experienced stroke center that has the proper equipment and trained staff. The treatment may be of benefit in other patients that also are not candidates for IV t-PA (Adams et al.). Currently research continues to investigate the benefits of combined IA/IV thrombolytic therapy along with other medical therapies such as clot retrieval and ultrasound (IMS II Trial Investigators, 2007; IMS Study Investigators, 2004; Khatri et al., 2008; Lewandowski et al., 1999). Not only are IA thrombolytics an option to increase the time window for intervention in acute ischemic stroke, clot retrieval is as well. Endovascular embolectomy has extended the time to intervention up to

8 hours in large artery occlusions accessible by a MERCI retriever (Smith et al., 2005), FDA-approved to remove clots from the intracranial arteries. As technology improves, newer generations of retrievers have emerged and shown even greater recanalization rates then previous models (Smith et al., 2008).

While research has brought about new treatment modalities for stroke, it has also unveiled new prevention options for patients with atrial fibrillation, PFO and carotid atherosclerosis. For patients with atrial fibrillation, the Maze procedure has shown to decrease the stroke and TIA rate compared to controls not receiving therapy by restoring sinus rhythm and by excision of the LAA (Cox et al., 1999). While new surgical techniques such as radiofrequency and cryoablation have been studied against the original incision-based Maze and said to require less time and skill (Lall et al., 2007), the two styles of surgical intervention have not shown to have clinically significant differing outcomes (Lall et al.; Sie et al., 2001). Magnetic guidance ablation and the radial approach are also possibilities for atrial fibrillation treatment (Faddis et al., 2002). As for procedures for the LAA, currently the ACC/AHA guidelines recommend appendage ligation during valvular procedures in the management of valvular heart disease to decrease thromboembolism risk but not for patients with atrial fibrillation (Bonow et al., 2008). Occlusion of the LAA may also eventually be an approved option for patients following completion of ongoing randomized trials of the WATCHMAN (Fountain et al., 2006).

For patients with PFO, research is still underway to bring about new interventions for prevention of stroke. Healthcare providers need to consider several anatomical variations in patients with PFO such as a coexisting atrial septal aneurysm, the degrees of shunting in the foramen, tunnel length and PFO size when considering the patients risks factors for stroke or

TIA for these factors have shown differing risk levels (Cabanes et al., 1993; Force et al., 2008; Goel et al., 2009; Homma et al., 2002; Mas et al., 2001). While the 2002 PICSS study showed medical treatment with aspirin or warfarin in PFO patients resulted in similar stroke rates between patients with and without PFO, healthcare providers should consider enrolling their patients in closure studies. Many trials are currently underway to compare medical therapy to closure of the atrial septal defect to determine if the new intervention has significant benefit over best medical therapy (Handke et al., 2007).

As for patients with carotid atherosclerosis, recommendations for preventative intervention do exist. At the current time, CEA has shown to be beneficial in symptomatic patients with stenosis, especially those with carotid stenosis >70% (Barnett et al., 1998). As mentioned previously, for those with recent stroke or TIA in the past 6 months and ipsilateral severe carotid stenosis of 70% to 99% stenosis, CEA is recommended to be performed by a surgeon with perioperative morbidity and mortality of <6%. For those with moderate stenosis (50% to 69%), CEA is recommended depending on factors such as patient age, gender, co-morbidities, and severity of initial symptoms (Sacco et al., 2006). As for those with asymptomatic carotid stenosis, the American Heart Association has found surgical treatment to be acceptable in patients with >60% stenosis, periopertaive risk <3% and life expectancy ≥5 years (Biller et al., 1998). While CEA has recommendations, CAS is still undergoing trials.

In conclusion, many considerations must be reviewed before choosing between new interventional techniques for the treatment and prevention of ischemic stroke. Patients may not be candidates for some of these interventions unless conventional treatment has already been attempted and failed, but for others these new interventional modalities may be their best hope of

effective therapy. As these modalities discussed in the review gain more popularity, more trials are beginning to test even more techniques that may be utilized in the future.

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Table 1

IV t-PA Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Age ≥18 years	Minor or rapidly improving symptoms or signs
Clinical diagnosis of stroke with a clinically meaningful neurologic deficit	CT signs of intracranial hemorrhage
Clearly defined time of onset of <180 min before treatment	A history of intracranial hemorrhage
A baseline CT showing no evidence of intracranial hemorrhage	Seizure at stroke onset
	Stroke or serious head injury within 3 months
	Major surgery or serious trauma within 2 weeks
	GI or urinary tract hemorrhage within 3 weeks
	Systolic BP >185 mmHg
	Diastolic BP >110 mmHg
	Aggressive treatment required to lower BP
	Glucose <50 mg/dl or >400 mg/dL
	Symptoms of subarachnoid hemorrhage
	Arterial puncture at a noncompressible site or lumbar puncture within 1 week
	Platelet count <100,000/mm3
	Heparin therapy within 48 hours associated with elevated activated PTT
	Clinical presentation suggesting post-MI pericarditis
	Pregnant women
	Anticoagulation due to oral anticoagulants (INR >1.7)

Note. Abbreviations as follows: CT = Computerized Axial Tomography scan; GI = gastrointestinal; BP = blood pressure; PTT = partial thromboplastin time; MI = myocardial infarction; INR = international normalized ratio. Information from "Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)," by G. W. Albers, P. Amarenco, J. D. Easton, R. L. Sacco, and P. Teal, 2008, *Chest, 133*(6 Suppl), p. 630S-669S.

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Abstract

Objective The purpose of this clinical review is to evaluate several options available for the treatment and prevention of acute ischemic stroke. ***Methods*** A clinical review was performed using MEDLINE and PubMed with the following search terms: *cerebral vascular accident, stroke*, *cerebral infarction, patent foramen ovale, atrial fibrillation, hypothermia, left atrial appendage, clot retrieval, MERCI, intra-arterial revascularization, stenting, and endarterectomy.* A search of UpToDate and AccessMedicine was utilized for background information. ***Results*** This review article includes information from 136 research articles in English. In addition to tissue plasminogen activator (t-PA), widely utilized for acute stroke treatment, more recent modalities include intra-arterial thrombolytics, mechanical clot retrieval, and therapeutic hypothermia. Secondary prevention is also growing with interventional procedures for atrial fibrillation, atrial septal defects, and carotid atherosclerosis. ***Conclusion*** Several of these treatment and prevention modalities are currently recommended in selected situations, whereas others remain in clinical trials reviewing safety and efficacy.