Stroke Intervention:  
*The Pros and Cons of rtPA*

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**I. Background**
Approximately 750,000 strokes occur each year in the US, accounting for the third leading cause of death and the chief cause of neurological debilitation (Go *et al.*, 2014). Strokes are caused by an interruption in the blood flow to the brain. Most commonly, the interruption in the blood flow is caused by a blockage of an artery supplying blood to a specific territory of the brain – a so-called “ischemic stroke”. Less commonly, bleeding can cause a stroke (deemed a “hemorrhagic stroke”).

Intravenous (IV) recombinant tissue plasminogen activator (rtPA) has been approved by the US Food and Drug Administration (FDA) for the treatment of acute ischemic strokes since 1996. Despite FDA approval twenty years ago, the efficacy of IV rtPA remains controversial, especially within the field of Emergency Medicine (EM) (Magid, Naviaux, & Wears, 2005; Zivin & Simmons, 2010). While in recent years the pendulum has swung more in favor of accepting its use as the standard of care, there remain a significant minority of opinion leaders in EM who believe the supporting evidence for treating stroke with IV rtPA is lacking and that the benefits (improved functional outcomes) are not outweighed by the risks (primarily intracranial hemorrhages).

Much stroke litigation revolves around the use of IV rtPA therapy, even though only about 6-8% of stroke patients are even eligible for treatment with rtPA (Demaerschalk *et al.*, 2016).

**II. Typical History and Symptoms Suggestive of an Ischemic Stroke**
Since an ischemic stroke is caused by the blockage of a blood vessel, the clinical presentation of an ischemic stroke will vary based on the blood vessel involved. The majority of blood flow to the brain travels in the so-called “anterior circulation”, which is supplied by the internal cerebral arteries and its branches. Strokes involving the anterior circulation typically present with one or more of the following symptoms: one-sided weakness opposite to the side of the stroke (typically the face and arm), one-sided sensory dysfunction opposite to the side of the stroke (typically numbness or tingling), preferential deviation of the eyes towards the side of the stroke, and some type of “cortical dysfunction”. When the left side of the brain is involved, the cortical dysfunction is typically language related (inability to produce or understand language correctly). When the right side of the brain is involved, patients most often present with neglect of their left hemi-space.

The “posterior circulation” is supplied by the vertebral arteries which combine to form the basilar artery. Strokes involving this part of the brain are typically more challenging to diagnose and manifest with a range of symptoms that can include a decreased level of consciousness, loss of balance or coordination, trouble walking, double vision, slurred speech, difficulty swallowing, vertigo, headache, and vomiting.

While certain presentation features are highly suggestive of a stroke due to bleeding, the only way to distinguish a hemorrhagic stroke from an ischemic stroke is to perform a non-contrast computerized tomography (NCCT) scan of the brain. Presentation features that suggest a stroke due to hemorrhage versus an ischemic stroke include decreased level of consciousness, elevated blood pressure, neurologic deficits that progress, headache, nausea and vomiting (Runchey & McGee, 2010).

**III. How an Ischemic Stroke Develops**
Most ischemic strokes are embolic strokes, meaning that the blood clot causing the stroke has dislodged from somewhere else, traveled in the bloodstream, and ultimately lodged in a blood vessel in the brain.
impeding blood flow beyond that point. The most common place blood clots dislodge from is somewhere in the heart or in one of the large blood vessels supplying blood flow to the brain, such as one of the internal carotid arteries. A smaller percentage of ischemic strokes are thrombotic strokes, which means the blood vessel becomes occluded at a site in which an atherosclerotic plaque has ruptured leading to formation of a clot there. In either case, the goal of acute ischemic stroke treatment with IV rtPA is centered at dissolving the blood clot which is impeding the blood flow.

IV. Diagnostic Criteria for an Ischemic Stroke

An ischemic stroke diagnosis, especially as it relates to treatment with IV rtPA, is essentially a clinical diagnosis that is supported by a NCCT scan of the brain. While a NCCT scan can demonstrate subtle early signs of an ischemic stroke, the most important reason to perform a brain NCCT scan in the clinical setting of an acute stroke is to exclude an intracerebral hemorrhage as the cause of the stroke. While advanced imaging beyond a NCCT of the brain is needed to make a determination to treat an ischemic stroke via an endovascular approach performed by a neurointerventional radiologist or neurosurgeon (a topic that is not discussed in this manuscript), the imaging standard for IV rtPA treatment decision making remains a NCCT (Demaerschalk et al., 2016).

V. How IV rtPA Can Improve a Stroke Patient’s Outcome

tPA is naturally synthesized and released by cells in the walls of blood vessels. It is responsible for most of the body’s natural efforts to prevent excessive blood clot formation, through dissolving clots that are no longer needed. Alteplase was the first rtPA and is identical to intrinsic human tPA. IV rtPA benefits patients by limiting the amount of brain tissue that dies, through dissolving a blood clot in an artery in the brain and restoring blood flow to the affected brain territory before it sustains irreversible damage. The therapeutic time window from the onset of a stroke to administration of IV rtPA is determined by 2 variables: (1) the absolute time from stroke symptom onset and (2) the degree of collateral circulation in the region of the brain affected by this stroke. While the degree of collateral circulation has the opportunity to improve outcome with delayed rtPA administration, the most critical factor for determining how beneficial IV rtPA treatment is likely to be is the time to administration from symptom onset (Muchada et al., 2014). The FDA, American Heart Association/American Stroke Association (AHA/ASA), and the American College of Emergency Physicians (ACEP) all recommend treatment with IV rtPA for an ischemic stroke patient within 3 hours of symptom onset (Brown et al., 2015; Demaerschalk et al., 2016). Beyond 3 hours from symptom onset, the recommendation of these 3 organizations differ. Even within three hours of symptom onset, there is disagreement between these organizations about what criteria may exclude a patient from IV rtPA eligibility. Many cases involving litigation for failure to treat with rtPA may center around these recommendations, so they are discussed further below.

VI. Historical perspective on IV rtPA for Ischemic Stroke

IV rtPA in the 0-3 hour window

In 1995, the results of the National Institute of Neurological Disorders and Stroke (NINDS) stroke trial were published (NINDS stroke study group, 1995). This trial essentially lead to the FDAs approval of rtPA for stroke after the trial was published. The NINDS stroke trial was a two part, randomized, double-blind trial of intravenous (IV) rtPA at a dose of 0.9 mg/kg versus placebo in patients with stroke symptoms within 3 hours of onset. It showed that patients who received IV rtPA within 3 hours of their stroke onset were at least
30% more likely to have little or no disability at 3 months, with an odds ratio for favorable outcome of 1.7. The main and undeniably most important risk this study identified relative to treatment with rtPA was bleeding in the brain associated with rtPA treatment, which was found in 6% of all patients treated.

Many opinion leaders, especially within EM, have been highly critical of rtPA’s approval by the FDA, and the influence that Genentech (the manufacturer of Alteplase in the US) has had in this arena over the past 20 years. The arguments that physicians have regarding the efficacy of rtPA treatment are numerous, but mostly involve insufficient scientific evidence and statistically flawed research trials involving IV rtPA (Dewey et al., 2010; Saver, Gornbein, & Starkman, 2010; Mann, 2006). While the overall trend has been in support of rtPA treatment over the last 20 years, this remains a polarizing issue among clinicians, especially among EM physicians. Moreover, recent changes in the FDA labeling for rtPA, and the AHA/ASA’s response to the FDA labeling changes, which are discussed below, have only fueled the controversy regarding rtPA.

rtPA in the 3-4.5 hour window

The third European Cooperative Acute Stroke Study (ECASS III) widened the potential window for treatment from 3 hours to 4.5 hours, with their published findings in 2008 showing that there was a more favorable outcome in patients treated with IV rtPA compared to placebo out to 4.5 hours from symptom onset (Hacke et al., 2008). The patient selection was slightly different from the NINDS trials, in that ECASS III excluded patients older than 80 years of age, had a combination of prior stroke and diabetes, and National Institute of Health Stroke Scale score greater than 25. Based on the results of the ECASS III trial, the AHA/ASA recommends that patients should be treated with IV rtPA in the 3-4.5 hour window, however they have recently suggested that even patients with some of the additional exclusion criteria that were a part of ECASS III are not necessarily contraindications for IV rtPA use (Demaerschalk et al., 2016). This remains a somewhat contentious issue. Furthermore, the FDA has not approved treatment with IV rtPA beyond 3 hours, citing insufficient scientific evidence supporting its use in this time window (Wechsler & Jovin, 2012).

Importance of expeditious treatment with rtPA

Although ECASS III showed some benefits to patients treated in the 3-4.5 hour time period, patients who were treated closer to the time of stroke onset tended to have better outcomes. Additionally, in a 2010 pooled analysis of the eight major randomized placebo-controlled trials of rtPA and acute ischemic stroke, investigators showed that the odds of a favorable outcome at 3 months decreased as the onset to time to treatment increased (Lees et al., 2010).

VII. Professional Guidelines Regarding IV rtPA Treatment for Acute Ischemic Stroke

The ACEP Clinical Policy for rtPA in Stroke

Because many EM physicians have been skeptical and consequently not committed to administering rtPA, for many years the ACEP policy on rtPA provided a viable defense for their position, indicating that rtPA should not be considered the standard of care for stroke. However, in February of 2013 ACEP, in conjunction with the American Academy of Neurology (AAN), promulgated a new rtPA policy stating that rtPA is an effective treatment for stroke, essentially erasing this line of defense for emergency physicians uncomfortable utilizing rtPA in the ED (Edlow et al., 2013). The 2013 ACEP/AAN policy stated that:

- In order to improve functional outcomes, IV rtPA should be offered to acute ischemic stroke patients who meet the defined eligibility criteria and can be treated within 3 hours after symptom onset; and
• IV rtPA **should be considered** in eligible patients if they can be treated within 3 to 4.5 hours after symptom onset.

It did, however, provide EM providers some latitude by noting that “the effectiveness of rtPA is less well established in hospitals without the systems in place to safely administer the medication.”

After publication of this policy, there was considerable upheaval among the ACEP membership regarding the scientific validity of the policy recommendations and perceived conflicts of interest among the 2013 clinical policy authors (Millard, 2013; Ellison, 2013). Based on the feedback ACEP received from its membership, ACEP took the unprecedented step of creating a new clinical policy committee and revising the clinical policy without collaboration with the AAN (Brown *et al.*, 2015). The revised 2015 policy states:

• With a goal to improve functional outcomes, IV rtPA **should be offered and may be given to** selected patients with acute ischemic stroke within 3 hours after symptom onset at institutions where systems are in place to safely administer the medication.

• Despite the known risk of symptomatic intracerebral hemorrhage and the variability in the degree of benefit in functional outcomes, IV rtPA **may be offered and may be given to** carefully selected patients with acute ischemic stroke within 3 to 4.5 hours after symptom onset at institutions where systems are in place to safely administer the medication.

**The FDA and rtPA for Stroke**

The only FDA approved indication for rtPA in acute ischemic stroke is within 3 hours of symptom onset. In 2011, Genentech (the pharmaceutical supplier for rtPA in the US) applied to the FDA to expand the IV rtPA indication to include treatment of patients up to 4.5 hours from stroke symptom onset. In 2012, the FDA decided to not approve Genentech's application to extend the therapeutic window for rtPA beyond 3 hours (Wechsler & Jovin, 2012). However, as part of this application process, Genentech took advantage of FDA changes in the content and format of prescribing information and significantly changed the labeling for rtPA use within 3 hours of symptom onset. The labeling changes included removing some contraindications and resulted in conflicting recommendations between the FDA labeling and the AHA/ASA recommendations. This resulted in the AHA/ASA publishing a scientific statement in 2016 that described their scientific rationale for the inclusion and exclusion criteria for IV rtPA for acute ischemic stroke (Demaerschalk *et al.*, 2016). How the FDA and ASA recommendations compare in the most important areas are listed in the tables that accompany this. Whether or not the areas of disagreement between the FDA labeling and AHA/ASA guidelines will be a focus of future litigation is unclear as of now.

**AHA/ASA Scientific Statement regarding IV RTPA in Acute Ischemic Stroke**

In September of 1996, the AHA/ASA published its first guidelines regarding rtPA for ischemic stroke. Those guidelines were updated in 2003, 2009, 2013, and 2016. In February 2016, when the AHA/ASA announced their most recent update, they boldly stated:

“This AHA/ASA statement writing group feels strongly that the AHA/ASA acute stroke management guidelines, in combination with the science presented in this statement, should be what clinicians access and apply to their acute ischemic stroke treatment and management decisions. This is especially true as the Prescribing Information changes were made by the FDA in the context of no substantial new information compared to the rigorous process undertaken by these authors.”

(Demaerschalk BM. International Stroke Conference, February 18, 2016 Los Angeles, CA).

While the AHA/ASA considers itself to be the organization that sets the standard for stroke care in the United States, many emergency medicine physicians disagree with the AHA/ASA's recommendations and feel they have been unduly influenced by Genentech.
VIII. Stroke Litigation Involving rtPA

Overwhelmingly, litigation involving IV rtPA for stroke is related to failing to treat with rtPA or delaying rtPA treatment, rather than for treating patients and having them sustain bleeding in the brain after rtPA treatment. This legal reality conflicts with the medicolegal fears most emergency medicine physicians have in this area, which is that they will be sued if they treat a patient with rtPA and the patient sustains subsequent bleeding in the brain (Brown et al., 2005).

Failure to treat with rtPA

A 2013 systematic review of stroke litigation cases involving rtPA and ischemic stroke showed that most cases involved emergency physicians, and that liability is most often associated with failure to treat with IV rtPA, rather than adverse events associated with its use (Bhatt et al., 2013). That study identified 789 ischemic stroke litigation cases, of which 46 cases were related to IV rtPA and stroke litigation. Case descriptions of 40 cases were available, while data for verdicts were available for 38 patients. The most frequent plaintiff claim was related to failure to administer IV rtPA (n=38, 95%). Only 2 (5%) claims involved complications of treatment with rtPA. Hospitals were defendants in majority of the 36 cases, while physicians were involved in 33 cases. EM physicians were involved in 25 (61%) cases, while neurologists were involved in 8 (20%) cases. There were 26 (65%) defendant-favored and 12 (30%) plaintiff-favored verdicts.

Similarly, Bambauer et al queried the LexisNexis Academic database for cases involving physicians and the use of rtPA in stroke (Bambauer et al, 2006). Most cases ended with a settlement and, therefore, were not publicly available, and the database contains mostly appellate level decisions. However, they were able to identify seven cases with final decisions. In all cases, claims were filed for the failure to administer rtPA, but only one of these cases favored the plaintiff.

In a 2008 review of lawsuits involving rtPA, Liang and Zivin identified 33 cases that involved rtPA and stroke (Liang & Zivin, 2008). More than half of these cases involved EM physicians and less than 20% involved neurologists. In every case in which a neurologist was a defendant, the EM physician was also named. In about two thirds of the cases, plaintiffs stated a failure or delay in diagnosis of stroke. In 88% of the cases, patients claimed there was a failure to treat with IV rtPA, whereas only 9% cited that the use of the drug caused their injury. In 12 of the 33 cases, the plaintiffs were given positive verdicts, with 2 of the 12 rewarded for injury from the use of the drug and the majority for failure to treat with rtPA.

Finally, in a search of state and federal cases, Thiess et al identified 20 trial court and six appellate cases that involved suits over the nonuse of IV rtPA for patients with a stroke, and none for injury caused allegedly by the drug (Thiess, Sattin, & Larriviere, 2010). In 14 of 20 cases, the verdict was for the defendant.

Since the majority of malpractice lawsuits involving rtPA for stroke allege failure to treat with rtPA, the data strongly suggest that patients sue because they were denied the opportunity to benefit from lytic therapy with rtPA (i.e., their “lost chance”). Traditionally, legal causation has been demonstrated by showing that there was a greater than 50% chance that the failure to administer a treatment caused the patient injury, but some courts will allow a plaintiff to recover for the “lost chance” for a better outcome (Hodson, 2007). The legal doctrine of lost chance has had a huge impact on medical malpractice litigation. Prior to adoption of “lost chance”, a medical expert was required to testify that “within a reasonable degree of medical certainty” there was a greater than 50% chance that the injury would not have occurred but for negligence. However, many jurisdictions now recognize an injury for negligence based upon a possible loss of a chance for a more favorable outcome. To complicate this issue, while most states recognize “lost chance”, some do not. Furthermore, how the theory is applied varies greatly in states that allow it. So under
this doctrine, a medical expert must merely testify that there was a chance, however slim in some states, for a better outcome.

**Delay in administering rtPA**

Since time to rtPA administration affects the efficacy of rtPA, some plaintiffs may claim that rtPA was not administered quickly enough, and that earlier administration of the drug would have led to a better outcome. This claim may be related to delay in recognition of the stroke at triage or by the emergency physician, delay in ordering or obtaining the CT scan and interpretation from the radiologist, or delay in ordering or actually administering the drug.

**IX. Summary**

Despite approval 20 years ago, rtPA treatment for ischemic stroke remains a contentious and somewhat polarizing issue among EM physicians and neurologists. Certainly, the recent FDA labeling changes and conflicts between the policy recommendations by ACEP and the AHA/ASA have only fueled the controversy in this area. To some extent, they represent significant changes in attitude and policy on the acute treatment of stroke with rtPA. These new policies may markedly change the landscape with respect to the standard of care and potential litigation in the care of stroke patients. However, it will likely take some time to elucidate their impact on the malpractice liability of hospitals and emergency physicians.

**X. Tables**

rtPA Contraindications **Retained** in the New FDA Physician Labeling, in which there is **Relative Agreement** with the ASA/AHA Recommendations*  

<table>
<thead>
<tr>
<th>FDA</th>
<th>2016 ASA/AHA IV rtPA Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current intracranial hemorrhage</td>
<td>Should not be administered <em>(Class III; Level of Evidence C)</em></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>Should not be administered <em>(Class III; Level of Evidence C)</em></td>
</tr>
<tr>
<td>Active internal bleeding</td>
<td>High risk and potentially harmful <em>(Class III; Level of Evidence C)</em></td>
</tr>
<tr>
<td>Recent intracranial or intraspinal surgery or serious head trauma (within 3 months)</td>
<td>Potentially harmful <em>(Class III; Level of Evidence C)</em></td>
</tr>
<tr>
<td>Bleeding diathesis</td>
<td>Safety and efficacy unknown, may be considered on a case-by-case basis <em>(Class IIb; Level of Evidence C)</em></td>
</tr>
<tr>
<td>Current severe uncontrolled hypertension</td>
<td>Recommended if BP can be lowered to &lt;185/110 mm Hg <em>(Class I; Level of Evidence B)</em></td>
</tr>
</tbody>
</table>


rtPA Contraindications **Removed** in the New FDA Physician Labeling, in which there is **Relative Agreement** with the ASA/AHA Recommendations*
<table>
<thead>
<tr>
<th>FDA</th>
<th>2016 ASA/AHA IV rtPA Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor neurological deficit or rapidly improving symptoms</td>
<td>Is indicated with mild but disabling stroke symptoms (<em>Class I; Level of Evidence A</em>).&lt;br&gt;Is reasonable for moderate to severe ischemic stroke demonstrating early improvement, but remaining moderately impaired and potentially disabled (<em>Class IIa; Level of Evidence A</em>).</td>
</tr>
<tr>
<td>Blood glucose level warnings</td>
<td>Is recommended with initial glucose levels &gt;50 mg/dL (<em>Class I; Level of Evidence A</em>).&lt;br&gt;May be reasonable with initial glucose levels &gt;400 mg/dL that are subsequently normalized (<em>Class IIb; Level of Evidence C</em>).</td>
</tr>
<tr>
<td>Severe neurological deficit (added to Adverse Reactions)</td>
<td>Is indicated despite increased risk of hemorrhagic transformation, due to proven clinical benefit (<em>Class I; Level of Evidence A</em>).</td>
</tr>
<tr>
<td>Major early infarct signs</td>
<td>Is recommended in the setting of early ischemic changes of mild to moderate extent (other than frank hypodensity) (<em>Class I; Level of Evidence A</em>).</td>
</tr>
<tr>
<td>Seizure</td>
<td>Is reasonable if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon (<em>Class IIa; Level of Evidence C</em>).</td>
</tr>
</tbody>
</table>


rtPA Contraindications **Removed** in the New FDA Physician Labeling, in which there is **Relative Disagreement** with the ASA/AHA Recommendations*

<table>
<thead>
<tr>
<th>FDA</th>
<th>2016 ASA/AHA IV rtPA Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent previous stroke (within 3 months)</td>
<td>May be harmful (<em>Class III; Level of Evidence B</em>). The potential for increased risk of sICH and associated morbidity and mortality exists but is not well established (<em>Class IIb; Level of Evidence B</em>).</td>
</tr>
<tr>
<td>History of ICH (moved to Warnings and Precautions and stated as recent ICH)</td>
<td>Potentially harmful (<em>Class III; Level of Evidence C</em>).</td>
</tr>
<tr>
<td>Examples of lab tests under bleeding diathesis Anticoagulants, INR, PTT Cutoff, or Platelet Count &lt;100,000</td>
<td>The safety and efficacy with platelets &lt;100,000/mm3, INR &gt;1.7, aPTT &gt;40 seconds, or PT &gt;15 seconds are unknown; Not recommended (<em>Class III; Level of Evidence C</em>).</td>
</tr>
</tbody>
</table>


## XI. References


