**Objectives**

1. Review medications US FDA approved for treatment of Acute Ischemic Stroke or Hemorrhagic Stroke
2. Describe specific considerations that must be evaluated prior to treatment of AIS with rtPA
3. Review recent clinical trials for medical and non-medical therapies for acute stroke
4. In the post acute transition of care after stroke list two modifiable risk factors to monitor the patient for
5. How many strokes occur every year in the USA
6. Why is it vital to administer rtPA quickly after AIS

**Abbreviations**

- AIS = Acute Ischemic Stroke
- ICH = Intracerebral Hemorrhage
- rtPA = Recombinant tissue plasminogen activator
- SAH = Subarachnoid Hemorrhage
- IVH = Intraventricular Hemorrhage
- AMM = Aggressive Medical Management
- PTAS = Percutaneous Transluminal Angioplasty and Stenting

**WHY STROKE**

Stroke is the 4th leading cause of death in the USA

Stroke is the leading cause of adult disability in the USA

Every year about 800,000 new or recurrent strokes occur

The annualized cost is estimated to be $75 billion in 2010

**World Stroke Organization**

Challenging age-old ideas about stroke

“But evidence is emerging from the USA (GC-NKY Study) that, while the incidence of stroke is falling in elderly people, there is a shift towards an earlier age at stroke onset and that incidence of stroke is rising in young adults”

Lancet Neurol 2012; 11: 1013
USA FDA APPROVED DRUG THERAPIES FOR STROKE

Acute Ischemic Stroke: List one approved drug?

Hemorrhagic Stroke: List one approved drug?

Acute Ischemic Stroke: Alteplase (rtPA) approved in 1996

Hemorrhagic Stroke: __________ approved in _____

Cerebrovascular Circulation

Arterial Circulation of the Brain, Including Carotid Arteries

Types of Stroke

15% Hemorrhage

85% Ischemic Stroke Subtypes

20% 25% 20% 30% 5%

Atherosclerotic CV disease
Penetrating Artery dz
Cardiogenic Embolism
Cryptogenic Stroke
Other Causes

Sources of Blood Clots to Brain

Stroke Images – AIS
**Sources of clot**

<table>
<thead>
<tr>
<th>Clot Source</th>
<th>Traditional Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial atherosclerosis</td>
<td>Anticoagulation + Stenting</td>
</tr>
<tr>
<td>Carotid plaque with emboli</td>
<td>EC-IC Bypass Surgery</td>
</tr>
<tr>
<td>Aortic Arch plaque</td>
<td>Risk Factor Modification</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>EC-IC Bypass Surgery</td>
</tr>
<tr>
<td>Small artery disease</td>
<td>Dual Antiplatelet Therapy</td>
</tr>
<tr>
<td>Cardiogenic emboli</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>Ventricular thrombi</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>Valve disease</td>
<td>Anticoagulation, Valve Repair</td>
</tr>
</tbody>
</table>

**Recent Clinical Trials for Stroke**

- **Thrombolysis with Alteplase 3 to 4.5 hours after AIS (ECASS III)**
- **Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID)**
- **Aspirin and ER Dipyridamole versus Clopidogrel for Recurrent Stroke (PROFESS)**
- **Effects of Clopidogrel added to Aspirin for recent Lacunar Stroke (SPS 3)**
- **Stenting vs Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS)**
- **Clopidogrel in High risk patients with Acute Non disabling Cerebrovascular Events (CHANCE)**
- **Interventional Management of Stroke (IMS 3)**

**Thrombolysis for AIS with Alteplase**

**Background**

- Alteplase (rtPA) was USA FDA approved in 1996 for AIS if administered within 180 mins of symptom onset based on the NINDS Study
- The NINDS Study randomized patients to IV rtPA or placebo
- More than 11,000 patients were screened and only 624 patients were randomized. Enrollment 11000 / 624 = 5.6%

**Results from NINDS Study**

![Image](image.png)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>rt-PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>26%</td>
<td>39%</td>
</tr>
<tr>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>21</td>
<td>17</td>
</tr>
</tbody>
</table>

**Modified Rankin Scores**

- NNTB = 100 / (39 - 26) = ~7.6
- This # includes 6.4% sICH rate

**Thrombolysis with Alteplase 3 to 4.5 hours after AIS (ECASS III)**

- The ECASS III Trial looked at the time window from 3 hrs to 4.5 hrs
- Patient were randomized to IV rtPA or placebo
- Significant Exclusions for ECASS III:
  - Severe stroke NIHSS > 25, Seizure at stroke onset, History of prior stroke and diabetes mellitus, SBP > 185 or DBP > 110, oral anticoagulant therapy, Age > 80 yo

**N Engl J Med 1995; 333: 1581-7.**

ECASS III Trial Results

### Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Score</th>
<th>Alteplase (N=415)</th>
<th>Placebo (N=607)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28.5</td>
<td>23.8</td>
</tr>
<tr>
<td>1</td>
<td>24.9</td>
<td>23.3</td>
</tr>
<tr>
<td>2</td>
<td>14.1</td>
<td>18.4</td>
</tr>
<tr>
<td>3</td>
<td>9.3</td>
<td>11.4</td>
</tr>
<tr>
<td>4</td>
<td>5.9</td>
<td>15.7</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>5.2</td>
</tr>
<tr>
<td>6</td>
<td>0.7</td>
<td>1.1</td>
</tr>
</tbody>
</table>

\[
\text{NNTB} = \frac{100}{(52.4 - 45.1)} \sim 14
\]

Specific considerations for Alteplase use prior to AIS

- Alteplase promotes thrombolysis by converting plasminogen to the active proteolytic enzyme plasmin
- Plasminogen is incorporated selectively into the thrombus and this results in minimal systemic effects
- Patients eligible for rtPA must have careful control of blood pressure prior to & for 24 hrs after rtPA administration
- rtPA is not given if the SBP > 185 or DBP > 110 mmHg

Alteplase for AIS, key criteria prior to administration

- Diabetic stroke
- The neurologic sign should not be elicited by an initially non-dominant digit
- The symptoms of stroke should not be suggestive of subarachnoid hemorrhage
- Close by symptoms <3 h before beginning treatment
- No head trauma or prior stroke in persons 7 months
- No symptomatic events from prior hemorrhage in process 31 days
- No major surgery within previous 30 days
- No recent major trauma in the previous 7 days
- Blood pressure not reduced (e.g., <110 mmHg systolic and diastolic <90 mmHg) after non-invasive treatment
- No evidence of active bleeding (i.e., acute trauma, head injury) on examination
- No history of active intracranial or extracranial bleeding in last 3 months
- If used by hospitals in process 48 h, OCCT in normal range
- Recent stroke <180 days
- CT scan does not show a clot, large hypodensities (such as >15% ventricles/hemispheres)

Comparison of Warfarin & Aspirin for symptomatic intracranial stenosis (WASID)

The WASID trial randomly assigned pts with TIA or Stroke with angiographically verified 50 to 99% stenosis of a major intracranial stenosis to receive warfarin (INR 2 to 3) or aspirin 1300 mg per day

The primary endpoint was ischemic stroke, brain hemorrhage or death from vascular causes other than stroke

After 569 pts were enrolled the study was stopped due to safety concerns in the warfarin group

Symptomatic Intracranial Disease

Background: Approximately 70000 to 90000 strokes / TIA’s occur every year due to intracranial arterial disease

The risk of recurrent stroke may be as high as 15% per year in this population

Traditional therapy has been anticoagulation since the 1950’s with retrospective studies suggesting warfarin may be more effective than ASA.

A survey in 2004 showed neurologists in the US were evenly split on the preference of warfarin or aspirin

Neurology 2004; 62: Supp 5: A266-A267
WASID Trial Results

Table 5. Subgroup Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>156 (9)</td>
<td>165 (11)</td>
<td>1.06 (0.87, 1.30)</td>
</tr>
<tr>
<td>Stroke</td>
<td>271 (16)</td>
<td>249 (14)</td>
<td>1.12 (0.91, 1.37)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>12 (1)</td>
<td>10 (1)</td>
<td>1.2 (0.7, 2.0)</td>
</tr>
</tbody>
</table>

Antiplatelet therapy after Stroke

Background: The Antithrombotic Trialist's Collaboration meta-analysis of 21 randomized trials compared antiplatelet therapy to placebo in 18,270 patients with prior stroke/TIA (not cardioembolic stroke)

28% relative (4% absolute) RR in nonfatal strokes
16% relative (7% absolute) RR in fatal strokes

Antiplatelet therapy after AIS –Recent Trials

Aspirin and ER Dipyridamole versus Clopidogrel for Recurrent Stroke (PROFESS)

This trial was a double blind, 2 X 2 factorial design. The groups were ASA-ERDP 25-200 1 bid, clopidogrel 75 mg daily, telmisartan 80 mg daily or placebo

The primary outcome was first recurrence of stroke

A total of 20,332 pts were enrolled and followed for a mean of 2.5 yrs

Aspirin + ER-DP vs Clopidogrel for Recurrent Stroke (PROFESS)

The study showed similar rates of stroke with ASA+ERDP and clopidogrel

The risk of major hemorrhage was similar in the two groups

Aspirin + ER-DP vs Clopidogrel for Recurrent Stroke (PROFESS)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASA + ER-DP (n=10,010)</th>
<th>Clopidogrel (n=10,010)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life threatening</td>
<td>96 (3)</td>
<td>49 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bleeding</td>
<td>40 (1)</td>
<td>25 (1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Symptomatic Intracranial bleeding</td>
<td>73 (2)</td>
<td>22 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>120 (3)</td>
<td>39 (1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Dual Antiplatelet Tx for AIS

Background: The MATCH trial compared clopidogrel + ASA to clopidogrel alone in stroke prevention or stroke.

7500 high risk pts were randomized to ASA 75 mg/day + Clopidogrel 75 mg/day vs. clopidogrel or placebo

Outcome | ASA + Clp | Clp | p value |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Life threatening</td>
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<tr>
<td>Major bleeding</td>
<td>120 (3)</td>
<td>39 (1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Effect of Clopidogrel added to Aspirin in Patients with Recent Lacunar Stroke (SPS 3)

Small lacunar strokes are particularly common in Hispanics and most result from intrinsic disease of the small vessels in the brain.

Pts with MRI identified symptomatic lacunar strokes were randomized to receive clopidogrel 75 mg/day + ASA 325 mg/day vs. ASA or placebo.

The trial enrolled 3020 pts with a mean follow-up of 3.4 years in North America, Latin America and Spain.

Results SPS 3 Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aspirin plus Placebo (N=1680)</th>
<th>Aspirin plus Clopidogrel (N=1637)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes (ischemic and hemorrhage)</td>
<td>158</td>
<td>17</td>
<td>0.80 (0.73-0.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>124</td>
<td>14</td>
<td>0.80 (0.69-0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>11</td>
<td>22</td>
<td>1.52 (0.74-3.10)</td>
<td>0.21</td>
</tr>
<tr>
<td>Subarachnoidal hemorrhage</td>
<td>0.12</td>
<td>0.13</td>
<td>1.25 (0.63-3.00)</td>
<td>0.62</td>
</tr>
<tr>
<td>Other</td>
<td>0.07</td>
<td>0.04</td>
<td>1.51 (0.51-4.49)</td>
<td>0.46</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.70</td>
<td>0.70</td>
<td>1.15 (0.99-1.33)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>0.52</td>
<td>0.50</td>
<td>1.18 (0.95-1.47)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Fatal hemorrhages</td>
<td>0.07</td>
<td>0.07</td>
<td>1.29 (0.75-2.24)</td>
<td>0.27</td>
</tr>
<tr>
<td>Intracranial</td>
<td>0.07</td>
<td>0.07</td>
<td>1.18 (0.51-3.12)</td>
<td>0.59</td>
</tr>
<tr>
<td>Extracranial</td>
<td>0</td>
<td>0.04</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Dual Antiplatelet Therapy for Long Term Stroke Prevention

Taken in conjunction with previous studies (MATCH, CHARISMA) the results of SPS 3 do not support the use of dual antiplatelet therapy for long term prevention of ischemic stroke.

Dual antiplatelet therapy results in higher rates of hemorrhage.

The SPS 3 showed higher mortality with dual antiplatelet therapy in patients after lacunar strokes.

What about dual antiplatelet therapy for shorter term stroke prevention?

Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial is ongoing in the USA - Patients randomized to clopidogrel 600 mg loading dose followed by 75 mg per day + / - Aspirin for 90 days.

Stenting vs Aggressive Medical Management for Intracranial Arterial Stenosis (SAMMPRIS)

Clopidogrel in High risk Acute Non disabling Cerebrovascular Events (CHANCE ) study recently completed in China.

Therapy for Intracranial Arterial Stenosis

Background: Atherosclerotic intracranial arterial stenosis is one of the most common causes of stroke and is associated with a high risk of recurrent stroke (Approx. 23% at 1 year).

Two strategies that have emerged are:
- Aggressive medical therapy (antiplatelet therapy + risk factor modification)
- Percutaneous transluminal angioplasty and stenting (PTAS)

The uncertainty of the superiority between medical therapy alone & PTAS prompted the SAMMPRIS Study.
Images - Intracranial Stenosis

90% Stenosis

Stenting vs Aggressive Medical Management for Intracranial Arterial Stenosis (SAMMPRIS)

Patients were randomized to AMM alone or AMM and PTAS with the use of Wingspan stent system

The primary endpoint was stroke or death within 30 days after enrollment or after revascularization procedure

Enrollment was stopped after 451 pts were randomized (Target was 764 pt’s)

SAMMPRIS -Aggressive Medical Management In Both Arms

Aspirin 325 mg / day for entire follow-up

Clopidogrel 75mg per day for 90 days

Aggressive, protocol driven risk factor management primarily targeting SBP < 140 mm Hg (130 mm Hg diabetics) and low density cholesterol < 70 mg / dl

Intervent USA – a lifestyle modification program

Antihypertensive agents, statin (Rosuvastatin), and antithrombolic agents provided free to patients

SAMMPRIS Results: 30 Day Outcomes

<table>
<thead>
<tr>
<th>PTAS</th>
<th>AMM</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or death</td>
<td>14.7%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Sympt. brain</td>
<td>30.3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Hemorrhage*

*Of 10 brain hemorrhages, 4 were fatal and 4 were disabling

PTAS = Percutaneous transluminal angioplasty & stenting

AMM = Aggressive Medical Management

SAMMPRIS Outcomes Expected vs Projected

Cumulative risk of stroke after a transient ischaemic attack (TIA) or minor stroke.
What about dual antiplatelet therapy for shorter term stroke prevention

The SAMMPRIS and CHANCE studies reveal that dual antiplatelet therapy may be more effective than single antiplatelet therapy for shorter term (< 90 days) stroke prevention

The ongoing POINT trial in the USA will further clarify the role of dual antiplatelet therapy

Clinical Pearl: Conversion of dual antiplatelet therapy to single antiplatelet therapy after 90 days is vital as longer term dual antiplatelet therapy has shown worse outcomes after stroke.

Acute Stroke therapy at the Crossroads

Endovascular treatment for AIS paralleled the testing of IV tPA in the 1980’s through 1990’s

Initially endovascular tx consisted of administration of fibrinolytic meds at the site of vascular occlusion

The Merci Concentric Retriever (2004) & Penumbra aspiration system (2007) were FDA approved via the 510k pathway for “removal of thrombus” within 8 hrs of stroke onset

JAMA 2011; 306: 2026-28
Endovascular Therapy (Devices)

FDA approval of the devices was based on single group nonrandomized trials comparing device treatment with historical controls

With the devices:
- Recanalization rates were higher than reported with rtPA
- Rates of symptomatic ICH were similar to rtPA
- Rates of good functional outcomes at 3 mo’s were worse than rtPA

Interventional Management of Stroke 3 (IMS 3) Study

A randomized, open-label trial to enroll pt’s with a NIHSS > 8 or greater treated within 3 hrs of symptoms. The aim of the study was to examine whether a combined intravenous (IV) and intra-arterial (IA) approach to recanalization is superior to standard IV recombinant tPA (rtPA) alone

The primary outcome is a favorable outcome in terms of functional independence as measured by a mRS score of 0 to 2 at three months

Int J Stroke 2008; 32:130-7

IMS 3 Study

90-Day Modified Rankin Scale Score Distribution

All Subjects

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV/IA Alone 85/14</td>
<td>12.8</td>
<td>15.6</td>
<td>16.3</td>
<td>17.1</td>
<td>15.8</td>
<td>8.8</td>
<td>20</td>
</tr>
<tr>
<td>Endovascular 34/15</td>
<td>15.9</td>
<td>11.1</td>
<td>16.4</td>
<td>14.9</td>
<td>7.1</td>
<td>22.4</td>
<td></td>
</tr>
</tbody>
</table>

Differences between the two treatment groups across the entire distribution of the mRS (p = 0.25, van Elterin test)

Broderick J. 2013 AHA Intl Stroke Conference

IMS 3 Study

Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Endovascular</th>
<th>IV t-PA alone</th>
<th>CMH p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within 7 days (%)</td>
<td>52 (12)</td>
<td>24 (10.8)</td>
<td>0.57</td>
</tr>
<tr>
<td>Death within 90 days (%)</td>
<td>83 (19.1)</td>
<td>48 (21.6)</td>
<td>0.52</td>
</tr>
<tr>
<td>Symptomatic ICH within 30 hours of IV t-PA initiation (%)</td>
<td>27 (6.2)</td>
<td>13 (5.9)</td>
<td>0.83</td>
</tr>
<tr>
<td>Asymptomatic ICH within 30 hours of IV t-PA initiation (%)</td>
<td>119 (27.4)</td>
<td>42 (18.5)</td>
<td>0.91</td>
</tr>
<tr>
<td>PH2 ICH identified within 31 hours (%)</td>
<td>25 (6.0)</td>
<td>13 (6.3)</td>
<td>0.90</td>
</tr>
</tbody>
</table>
Intracranial atherosclerosis
- Anticoagulation + Stenting
- Antiplatelet therapy

Carotid plaque with emboli
- EC-IC Bypass Surgery
- Medical therapy

Aortic Arch plaque
- Risk Factor Modification

Carotid stenosis
- EC-IC Bypass Surgery
- Medical Therapy

Small artery disease
- Dual Antiplatelet Therapy
- Single antiplatelet therapy

Sources of clot

Traditional Therapy

New Therapy

Cardiogenic emboli
- Anticoagulation

Ventricular thrombi
- Anticoagulation

Atrial Fibrillation
- Anticoagulation

Valve disease
- Anticoagulation, Valve Repair

? Other
- Endovascular Therapy +/- rtPA
- Medical Therapy +/- rtPA

World Leaders and Stroke

10 of 43 US Presidents have suffered strokes

Many suffered the stroke after leaving office

When Woodrow Wilson had a stroke his wife Edith took over and completed the term

Ariel Sharon (former Prime Minister of Israel) had a small stroke in 2005. He was found to have a small PFO and his MRI showed he had amyloid angiopathy (blood vessels in the brain are weakened with an increase in the risk of bleeding). He was discharged on enoxaparin and scheduled for an elective cardiac cath. to repair the PFO. The night before the surgery he had a massive brain ICH and has since been in a persistent vegetative state

Conclusions

Today we remain with ONLY 1 US FDA approved drug therapy for acute stroke

Clinical trials over the last few years have yielded interesting and many times unexpected results

In specific stroke subtypes we have a lot of new information to guide use and selection of medical and non-medical therapy

Stroke Prevention by aggressive risk factor modification (e.g. blood pressure control, smoking cessation, control of hyperlipidemia) are paramount measures to reduce the burden of this devastating disease