Stroke Care Innovations and Best Practices

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Professor and SA Vice-Chair of Neurology
Director, Comprehensive Stroke and Vascular Neurology Program
Outline

• Epidemiology
• Diagnosis
• Prevention
  » Diet
  » BP lowering
  » Antithrombotics
  » Transient ischemic attack
  » Cholesterol lowering
  » PFO closure
  » Hypertensive Encephalopathy
• Acute Treatment
  » Supportive care
  » Deter clot propagation
  » IV lytics
  » Endovascular thrombectomy
  » Regional systems of care
  » COVID Era
Epidemiology
Worldwide Impact of Stroke

• First leading cause of serious disability
  » Over 16 million strokes / year, including over 10 million nonfatal strokes / year

• Second leading cause of death
  » Over 6 million deaths / year
  » 10% of all deaths worldwide

• Second leading cause of dementia

• 85% of the disease burden of stroke borne by low-income and middle-income countries


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Changing Incidence Due to Advances in Prevention / Acute Rx

Tremendous Reduction in Age-Adjusted Stroke Mortality (and Dementia)

1900-2014: Stroke Mortality ↓86%

1960-2010: Stroke Mortality 3rd to 4th (to 5th)

1960-2005: Recurrent stroke RCT controls ↓50%

1975-2008: Dementia incidence ↓44%

--Hong + Saver, et al, Circulation 2011

--Satizabal et al, NEJM 2016

--Towfighi + Saver, Stroke 2011
But Stroke Is an Age-Related Disease And More People are Becoming Older

- Stroke occurs throughout lifespan
  - Fetal life (cerebral palsy)
  - Pediatric
  - Young Adulthood
  - Midlife
  - Elderly
- But incidence doubles in every decade of life
- Two-thirds of strokes in US in >65 yos
### Stroke Subtypes in Large US Studies

<table>
<thead>
<tr>
<th>Ischemic Stroke (83%)</th>
<th>Hemorrhagic Stroke (17%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large Artery</strong></td>
<td><strong>Intracerebral Hemorrhage (70%)</strong></td>
</tr>
<tr>
<td>Atherothrombotic (25%)</td>
<td></td>
</tr>
<tr>
<td>Small vessel disease</td>
<td><strong>Subarachnoid Hemorrhage (30%)</strong></td>
</tr>
<tr>
<td>(“lacunar”) (20%)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardioembolic</strong></td>
<td></td>
</tr>
<tr>
<td>(25%)</td>
<td></td>
</tr>
<tr>
<td><strong>PFO-Associated</strong></td>
<td></td>
</tr>
<tr>
<td>(5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Other Defined</strong></td>
<td></td>
</tr>
<tr>
<td>(10%)</td>
<td></td>
</tr>
<tr>
<td><strong>Cryptogenic</strong></td>
<td></td>
</tr>
<tr>
<td>(15%)</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis
Bioenergetic Compromise

Hemodynamic Compromise

Steno-Occlusions/Malformations

Tissue Status

Perfusion Status

CTA

PCT - rCBF

PCT - Tmax

DWI

PWI

Multimodal CT

SAH

ICH

AIS

Multimodal MRI

SAH

ICH

AIS

Stroke Type

Vessel Status

Tissue Status

Perfusion Status

SAH

ICH

AIS

Steno-Occlusions/Malformations

Bioenergetic Compromise

Hemodynamic Compromise

SAH

ICH

AIS
Diagnostic Assessment for Ischemic Stroke Mechanism

• Characterize
  1. Stroke topography
  2. Aortocervicocephalic arteries
  3. Structural cardiac disease
  4. Cardiac dysrhythmias
  5. Hematologic disorders

Ambulatory Cardiac Monitoring Technology

• 1940s
  » 75 lb backpack
• 1980-2010
  » Miniaturized, 24h standard
• 2010 – 2017
  » Mobile cardiac outpatient telemetry systems
    • Monitor or patch, 2-4 wks
  » Loop recorders
    • External, event monitors, 2-4 wks
    • Implantable SQ, 1-3 yrs
• 2015 – 2017
  » Smartphones, AliveCor iOS app
    • User-initiated
    • Lifelong
• 2017 – 2020
  » Smartwatches, smartbands
    • Continuous, automated AI detection
    • Lifelong
• 2021 – 2030
  » Smart clothes - Lifelong

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Occult AF in Cryptogenic Stroke
(Evident Only After Prolonged Monitoring)

- **Meta-analysis**
  - 20 studies, 1723 patients
  - MOCT – 15.3%
  - External loop – 16.2%
  - Implantable loop – 16.9%
  - Total – 16.9%

- **Low burden AF**
  - 1 in 6 patients
  - Even in those patients, causal relation uncertain

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--Sposata et al, Lancet Neurol 2015
Prevention
Differential CV Risk Factor Contributions to Stroke and MI
Population Attributable Risk in ~60,000 Patients from 52 Countries

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--INTERSTROKE, Lancet 2016; INTERHEART, Lancet 2004
Preventive Stroke Therapies: Overview

**Behavior / Lifestyle**
- Healthy diet
- Aerobic exercise
- Healthy weight
- Avoid tobacco
- Limit alcohol
- Avoid extreme stress

**Pharmacologic**
- **Atherosclerosis**
  - Antiplatelets
  - BP lowering
  - Cholesterol lowering
- **Cardioembolism**
  - Anticoagulants
    - Vit K-dependent
    - DOACs
- **Other, e.g.**
  - Immunomodulatory (vasculitis)
  - Anti-migraine (migraine-induced stroke)

**Surgical/Procedural**
- **Atherosclerosis**
  - Cervical carotid (freq)
  - Endarterectomy
  - Stenting/plasty
- **Cardioembolism**
  - Atrial fibrillation
  - Ablation / MAZE
  - LAA occluders
  - Patent foramen ovale
  - PFO occluders

*All Stroke Ischemic + Hemorrhagic*

*Ischemic Stroke*
1. Diet and Lifestyle
1 - Diet and Lifestyle Change

- **Tobacco**
  - None/ quit ≥ 12 mos

- **Physical activity**
  - 150 mins/wk moderate, or
  - 75 mins/wk vigorous

- **Healthy weight**
  - < 25 kg/m2

- **Healthy Diet**
  - 4-5 of 5 components*

- **Blood pressure**
  - <120/80

- **Cholesterol**
  - Tchol < 170 mg/dl

- **Blood glucose**
  - Fasting < 100 mg/dl

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Cardiovascular Risk per Life’s Simple 7 and New Stroke in African-Americans

--Foraker et al, Am Heart J 2016
RCT – Confirmed Diet and Behavior Change for Stroke Prevention

- **Diet**
  - **Food-based**
    - Mediterranean - 1 positive long-term RCT
  - **Nutrient-based**
    - Low fat – 1 negative long-term RCT
    - Low carb – no long-term RCT

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--Mozaffarian, Circulation 2016
RCT – Confirmed Diet and Behavior Change for Stroke Prevention

• Diet
  » Food-based
    • Mediterranean - 1 positive long-term RCT
  » Nutrient-based
    • Low fat – 1 negative long-term RCT
    • Low carb – no long-term RCT

• Behavior change
  » Specific, proximal, shared goals
  » Self-monitoring
  » Scheduled follow-up
  » Regular feedback
  » Self-efficacy (belief one can succeed)
  » Motivational interviewing
  » Family and peer support
  » Multicomponent approaches

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--Mozaffarian, Circulation 2016
2. Blood Pressure Lowering
Stroke Mortality and Blood Pressure
61 Prospective Studies, 1 Million Persons
--Prospective Studies Collaboration, Lancet 2002
## 2 – Blood Pressure Lowering

Updated ACC/AHA Guidelines

<table>
<thead>
<tr>
<th></th>
<th>JNC 7</th>
<th>2017 ACC/AHA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition of HTN</strong></td>
<td>≥ 140</td>
<td>≥ 130</td>
</tr>
<tr>
<td><strong>Start of Antihypertensive Medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Population</td>
<td>≥ 140</td>
<td>≥ 140</td>
</tr>
<tr>
<td>Diabetes or CKD</td>
<td>≥ 130</td>
<td>≥ 130</td>
</tr>
<tr>
<td>Age ≥ 65 or High CV Risk</td>
<td>--</td>
<td>≥ 130</td>
</tr>
<tr>
<td><strong>Treatment Goal with Medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Population - SBP</td>
<td>&lt; 140/90</td>
<td>&lt; 130/80</td>
</tr>
<tr>
<td>Diabetes or CKD</td>
<td>&lt; 130/80</td>
<td>&lt; 130/80</td>
</tr>
</tbody>
</table>

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3. Antithrombotics
The Two Processes of Thrombus Formation: White Clots and Red Clots

• “White clots”
  » Platelet rich with some fibrin strands
  » Form in settings of high speed, dyslaminar flow, shear stress
  » Driving force: platelet activation and aggregation
  » Rx: Antiplatelet

• “Red clots”
  » RBC rich with dense fibrin strands
  » Form in settings of stasis (venous, A fib, very slow arterial flow)
  » Driving force: clotting protein cascade
  » Rx: Anticoagulant

Transient Ischemic Attacks

• “A transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.”
  » Symptoms most commonly 5-30 mins, can be up to 24h
• May occur with any cause of ischemic stroke
  » Large artery atero > lacune > cardioembolic
• After TIA, ten times the risk of ischemic stroke
  » Risk highest in first 3 months following TIA
  » 35% stroke risk within 3-5 years after TIA
• Rapid work-up and start of secondary prevention treatment has reduced recurrence rates by 50-80%

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Selective Short-Term DAPT to Prevent Early Recurrent AIS

- Selected AIS patients
  - Etiology - Non-cardioembolic
  - Severity - Minor AIS or TIA
    - Low NIHSS (e.g. 0-4)
    - Small infarct (e.g. <1.5 cm)
- ↑ risk of recurrent AIS > ICH during 1st 3 weeks
- Regimens
  - Clopidogrel + ASA
  - Dipyridamole + ASA
  - Cilostazol + ASA
  - Ticagrelor + ASA

--Albay et al, BMC Neurol 2020
4. Cholesterol Lowering
Statins for Secondary Prevention of Recurrent Stroke

“AHA/ASA 2° Prevention Guideline 2014

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

“Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin…”

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Frequency of Atherosclerosis as Cause of Ischemic Stroke

Atherosclerotic Origin – 70%

- Large Artery Athero - 30%
  - Cervical – 15%
  - Intracranial – 10%
  - Aorto-thoracic – 5%

- Small Artery Athero – 20%
  - Microatherosclerosis – 15%
  - Ostial parent artery athero – 5%

- Cardiac related to CAD – 20%
  - A fib – 12%
  - Post-MI / ↓LVEF – 8%

Non-Atherosclerotic Origin- 30%

- Nonatherosclerotic arteriopathies – 5%
  - Dissection
  - FMD
  - CADASIL
  - Vasculitis
  - Moyamoya, etc

- Cardiac not related to CAD – 10%
  - Endocarditis
  - Mechanical valve
  - Viral cardiomyopathy
  - A fib/SSS due to conduction aging
  - Myxoma, etc

- Vasospasm – 2%
  - RCVS
  - Eclampsia, etc

- Hypercoagulable arterial state – 2%
- Transcardiac – PFO. Pulm shunt, etc – 3%
- Cryptogenic – 8%

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**Consequences of Statin Overuse in Ischemic Stroke Patients**

If all ischemic stroke on statin in US: 660,000 x 0.3 = 198,000 without indication

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Absolute Increase in Statin Users*</th>
<th>Avoidable Side Effects Among 198,000 IS per yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>4%</td>
<td>7900</td>
</tr>
<tr>
<td>Myopathy</td>
<td>0.15%</td>
<td>300</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0.01%</td>
<td>20</td>
</tr>
<tr>
<td>New Onset Diabetes</td>
<td>0.2% per year</td>
<td>400 per year</td>
</tr>
<tr>
<td><strong>Total in 1 Year</strong></td>
<td><strong>4.2% in 1 year</strong></td>
<td><strong>8300</strong></td>
</tr>
</tbody>
</table>

*Banach et al. Statin intolerance - Archives of Medical Science 2015

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PCSK9 Inhibitors

- Monoclonal antibody agents
  - Evolocumab (Repatha)
  - Alirocumab (Praluent)
- Initially trials in familial hypercholesterolemia
  - FDA approved 2015
  - Pricing ~$14,000/yr
- For ASCVD
  - FOURIER trial 2017
  - FDA approved (evo) 2018
  - Pricing – evolving
    - Express scripts May 2018: $4,500 to $8,00/yr
Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) Trial
--Sabatine et al, NEJM 2017

- 27,564 patients
  » 1242 sites, 49 countries
- Entry criteria
  » Symptomatic ASVD
    • MI, Ischemic stroke of athero origin (19.4%, 5337), OR Peripheral arterial disease
  » Additional risk factors
    • At least 1 of 6 major RFs, or
    • At least 2 of 6 minor RFs
  » LDL ≥ 70 or HDL ≥ 200 on statin
    • Mean LDL 92
- SQ PCSK9 or placebo 1x per month
  » LDL during trial
    • 30 (IQR 19-46) [vs 90]
    • ≤ 25 in 42% [vs 0.1%]

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--FOURIER, NEJM 2017
--Pedersen et al, FOURIER: Focus on Cerebrovascular Disease, Eur Soc Cardiol 2017
Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) Trial
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    • ≤ 25 in 42% [vs 0.1%]

Key 2º Endpoint
CV Death, MI, Stroke

NNT to prevent 1 event over 3 years: 50
FOURIER and Stroke as Qualifying Event

--Primary Endpoint: CV Death, MI, Stroke, Unstable Angina, Coronary Revascularization
--Key Secondary Endpoint: CV Death, MI, Stroke

--Giugliano et al, Stroke 2020
When to Use PCSK9 Inhibitors (Provisional)

1. “Statin Failure”: ischemic stroke or highly probable TIA of atherosclerotic origin while on moderate-high dose statin, OR

2. “High Risk Statin Naive”: ischemic stroke or highly probable TIA of atherosclerotic origin while on no or low dose statin, and 1 of:
   1. Severe 70-99% vertebrobasilar LAAD
   2. Severe 70-99% anterior intracranial LAAD
   3. Severe ascending/transverse aortic LAAD
   4. Familial dyslipidemia

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5. PFO-Associated Stroke
Caught in the Act: Rare but Convincing
PFO Closure vs Medical Therapy - Recurrent Ischemic Stroke

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Device + MT</th>
<th>Medical Therapy</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Pt-Yrs (Pts)</td>
<td>Events</td>
</tr>
<tr>
<td>Umbrella-clamshell devices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLOSURE</td>
<td>-0.11</td>
<td>0.40</td>
<td>12</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>12</td>
<td>789 (447)</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double disk devices (all or predominantly)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC</td>
<td>-1.97</td>
<td>1.09</td>
<td>1</td>
</tr>
<tr>
<td>RESPECT-Extended</td>
<td>-0.60</td>
<td>0.30</td>
<td>18</td>
</tr>
<tr>
<td>CLOSE</td>
<td>-3.51</td>
<td>1.11</td>
<td>0</td>
</tr>
<tr>
<td>REDUCE</td>
<td>-1.47</td>
<td>0.50</td>
<td>6</td>
</tr>
<tr>
<td>DEFENSE-PFO</td>
<td>-2.40</td>
<td>1.47</td>
<td>0</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>25</td>
<td>6780 (1442)</td>
<td>66</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.61; Chi^2 = 9.46, df = 4 (P = 0.05); I^2 = 58%
Test for overall effect: Z = 3.20 (P = 0.001)

Total (95% CI) | 37        | 7579 (1889) | 79       | 6227 (1671) | 100.0% | 0.30 [0.13, 0.68] |

Heterogeneity: Tau^2 = 0.54; Chi^2 = 13.52, df = 5 (P = 0.02); I^2 = 63%
Test for overall effect: Z = 2.89 (P = 0.004)
Test for subgroup differences: Chi^2 = 5.38, df = 1 (P = 0.02); I^2 = 81.4%

---Saver, Mattle, Thaler, Stroke 2018

**Double disk devices**
- HR, 0.20; 95%CI 0.08–0.54, P=0.001
- Over 5 years: 1.8% vs 6.0%, NNT 24
Proportion of CS patients with incidental PFO

**Case A**
Proportion of CS patients with PFO: 40%
Proportion of controls with PFO: 25%

- Patients with CS & PFO (50% of PFOs are incidental)
- Patients with CS unrelated to PFO (PFO rate=25%, identical to controls)

Probability PFO is incidental in CS cases:

\[
\frac{\text{Prevalence of PFO in controls} \times (1 - \text{Prevalence of PFO in CS cases})}{\text{Prevalence of PFO in CS cases} \times (1 - \text{Prevalence of PFO in controls})}
\]

How Often is a PFO Causally-Related to Cryptogenic Ischemic Stroke?

<table>
<thead>
<tr>
<th></th>
<th>Case control studies</th>
<th>Cryptogenic Stroke (unadj)</th>
<th>Known Cause Stroke (unadj)</th>
<th>RR (Pub Bias Adj)</th>
<th>95% CI (Pub Bias Adj)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 55 yo</td>
<td>11</td>
<td>56%</td>
<td>14%</td>
<td>2.32</td>
<td>(1.74-3.11)</td>
</tr>
<tr>
<td>≥ 55 yo</td>
<td>9</td>
<td>25%</td>
<td>12%</td>
<td>2.51</td>
<td>(1.69-3.74)</td>
</tr>
</tbody>
</table>

Bayes’ Theorem

### How Often is a PFO Causally-Related to Cryptogenic Ischemic Stroke?

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Case control studies</th>
<th>Cryptogenic Stroke (unadj)</th>
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</tr>
</tbody>
</table>

**Bayes’ Theorem**

- PFOs cause
  - ~38% of cryptogenic IS in young and middle-aged adults
  - ~10% of all IS in young and middle-aged adults
  - ~5% of all IS

---

Proposed Flexible Clinical Practice Approach to Classifying PFO Causal Relatedness

In Patients with Embolic Infarct Topography AND without Other Major Stroke Sources

<table>
<thead>
<tr>
<th>Risk Grade</th>
<th>Features</th>
<th>Causal Relatedness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low RoPE Score</td>
</tr>
<tr>
<td>Very high risk</td>
<td>PFO + straddling thrombus</td>
<td>Definite</td>
</tr>
<tr>
<td>High risk</td>
<td>BOTH of: 1A. PFO + ASA, or 1B. Large shunt PFO, AND 2. PE or DVT preceding index infarct</td>
<td>Probable</td>
</tr>
<tr>
<td>Medium risk</td>
<td>ANY of: 1. PFO + ASA 2. Large shunt PFO</td>
<td>Possible</td>
</tr>
<tr>
<td>Low risk</td>
<td>Small shunt PFO w/o ASA</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

*High RoPE Score: ≥ 7


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Hypertensive Encephalopathy

• Mechanism: Results from hyperperfusion of brain when upper limit of autoregulation exceeded
  » Cerebral edema, petechial hemorrhages, microinfarcts
  » Typically SBP >220

• Symptoms
  » Severe h/a, N/V, visual disturbances, confusion, focal or generalized weakness, seizures

• One form of posterior reversible encephalopathy (PRES)

• Largely reversible with reduction in BP
Hypertensive Encephalopathy

- After acute episode, increased long term risk for:
  - Recurrent hypertensive encephalopathy
  - Stroke
    - Intracerebral hemorrhage
    - Ischemic stroke
  - Other end organ malignant hypertension events
- But risk low with treatment of underlying cause of hypertension
  - Renal artery stenosis
  - Eclampsia
  - Pheochromocytoma
  - Essential HTN/non-adherence
  - Etc:

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Treatment of Acute Ischemic Stroke
Five Major Strategies to Treat Acute Ischemic Stroke

- Supportive Care
- Avert Clot Propagation
- Recanalization
- Collateral Enhancement
- Neuroprotection

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Early Supportive Acute Stroke Care

5-15% Increase in Good Outcomes in Acute Stroke Unit Controlled Trials

• Treat hypoxemia
  » Continuous pulse oximetry, supplemental oxygen as needed
• Maintain normothermia
  » Early antipyretics/antibiotics
• Avoid hyperglycemia
  » Avoid glucose infusions/use SSI/maintain glucose < 200 mg/dl
• Early parental fluid to support collaterals
  » Maintenance normotonic IV fluids (IV NS 75-100 cc/h)
• Permissive hypertension to support collaterals
  » Treat only if >220/120 (lower if tPA)
• DVT prophylaxis
  » Compression boots/hep/LMWH
  » Early mobilization
• Early swallow assessment to guide oral feeding

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Preventing Clot Propagation
Antithrombotics and Acute Ischemic Stroke

• **Aspirin**
  - 4 trials, 41,291 patients
  - Minimally beneficial
  - Disability or death
    - 45.0% vs 46.2%, OR = 0.95 (95%CI 0.91-0.99)
    - NNT: 84

• **Heparin/LMWHs**
  - 24 trials, 23,748 patients
  - No net benefit

---

_Sandercock et al, Cochrane 2014 (AP) / Sandercock et al, Cochrane 2015 (AC) / Al-Ajlani et al, Neurovasc Imag 2017_
The Ischemic Penumbra

Irreversible Core Infarct

Ischemic Penumbra
zone of salvageable tissue surrounding core infarct
Irreversible Infarct Core Grows into Penumbral Zone
In a typical acute ischemic stroke, every minute the brain loses:

- 1.9 million neurons
- 14 billion synapses
- 7.5 miles myelinated fibers

-- Saver, Stroke 2006
Minutes Matter

• IV TPA
   » Every 8 minute delay causes 1 fewer of 100 treated patients to benefit in improved ambulation

• IA Neurothrombectomy
   » Every 4 minute delay causes 1 fewer of 100 reperfused patients to benefit in reduced final disability

Warning Signs and Activation of EMS System

SPOT A STROKE
FAST
FACE DROOPING
ARM WEAKNESS
SPEECH DIFFICULTY
TIME TO CALL 911

Signs of a Stroke
BE FAST and call 911

¿Será que es un STROKE?
(ATAQUE CEREBRAL)

¡Sí! ¡Es hora!
¡Actúa! ¡Al 911!

Será que é um STROKE?
Edema Vascular Central (Trombo ou Descarranho)

AST
FACE
ARM SPEECH TIME
THINK

Será que é um STROKE?
Diz coisas estranhas quando FALÁ?
Pode-á para repetir uma frase.

Não consegue manter um BRAÇO levantado?
Pode-á para levantar os braços.

Um lado do ROSTO está caindo?
Pode-á para sorrir.

Se você responder SIM a Qualquer uma dessas perguntas e HORA de agir rapidamente;
Ligue para 911 e diga "STROKE!"

UCLA Stroke Center
Race/Ethnic and Sex Differences in EMS Transport for Stroke

- 398,798 stroke patients
- 1613 GWTG-Stroke hospitals
- Overall, 59% of stroke patients arrived via EMS
- After adjustment for patient characteristics:
  - Hispanic men and women, Asian men and women, and black women had 20%-29% lower odds of using EMS

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UCLA Stroke Center

--Mochari-Greenberger et al, JAHA 2015
AI to Increase EMS Activation
Ubiquitous Monitoring and Ambient Intelligence
Accelerated Stroke Onset Detection

Las Vegas Casinos

Home Cameras/Voice Assistants
Home Health Robots
Smart Phones

Accelerometer and Computer Vision - Fall Detection

---Example: Leone et al. Detecting falls with 3D range camera in ambient assisted living applications. Medical Engineering & Physics 2011
Target: Stroke
Best Practice Strategies

1. *EMS Pre-Notification
2. Stroke Toolkit
3. Rapid Triage and Stroke Team Notification
4. *Single Call Activation System
5. *Transfer Directly to CT
6. Rapid Brain Imaging
7. *POC Laboratory
8. *Premix TPA
10. Team approach
11. *Prompt data feedback
IV TPA Under 3 Hours – Patient Education

- Joint AHA-AAN-ACEP text tool to educate patients and families
- UCLA icon array tool based on AHA-AAN-ACEP

--Gadhia et al, Stroke 2010
Time Trend in the Proportion of Patients with DTN Times within 45 Minutes Pre-Target: Stroke and During Target: Stroke Phase I and II

<table>
<thead>
<tr>
<th>Time Period (per year)</th>
<th>Estimate (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Target: Stroke</td>
<td>0.12 (-0.20, 0.43)</td>
<td>0.4741</td>
</tr>
<tr>
<td>Target: Stroke Phase I</td>
<td>2.87 (2.49, 3.25)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Target: Stroke Phase II</td>
<td>10.20 (5.92, 14.48)</td>
<td>0.0018</td>
</tr>
</tbody>
</table>
Target: Stroke Phase 3

- Intravenous
  - Primary
    - DTN ≤ 60m in 85%
  - Secondary
    - DTN ≤ 45m in 75%
    - DTN ≤ 30m in 50%

- Endovascular
  - Door to Device (DTD)
    - EMS: DTD ≤ 90m in 50%
    - Tx: DTD ≤ 60m in 50%

*Door-to-device: arrival to first pass of thrombectomy device*
Mobile Stroke Units for Prehospital Thrombolysis

--Walter et al, PLOS One, 2010, Homburg

--Audebert et al, Berlin
World Map of Mobile Stroke Unit Projects

- Active
  - 22 Units
  - 16 cities
  - 5 continents

- In Process
  - 13 Units
  - 12 cities

- Sites with active mobile stroke units
- Sites with projects in planning or implementation state

Modified from Lesmeister/Fassbender 2018
Dispatcher impression: Stroke

Provider impression: Stroke

NIHSS: 7
LAMS: 3

Clinical scenario: 76 year old woman with history of prior TIA (lip numbness & dysarthria 5 month prior), presenting with witnessed acute onset left face/arm weakness, difficulty with ambulation

Acute NIHSS 7: left face/arm weakness, numbness, ataxia, dysarthria, sensory

LKWT-to-Tx time: 45 min
MSU admission-to-CT time: 5 min
MSU admission-to-needle time: 19 min

24 hr NIHSS 1: mild sensory deficit in left arm
# B_PROUD Trial
## Treatment Process Differences

<table>
<thead>
<tr>
<th></th>
<th>MSU Not Available (n=794)</th>
<th>MSU Available (n=749)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated on MSU</td>
<td>0%</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>tPA treatment rate</td>
<td>48%</td>
<td>60%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time - Alarm to tPA, median</td>
<td>70 min</td>
<td>50 min</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time - LKW to tPA, median</td>
<td>110 min</td>
<td>95 min</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>tPA within 60 min of LKW</td>
<td>4%</td>
<td>13%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Endovascular thrombectomy</td>
<td>13%</td>
<td>14%</td>
<td>0.65</td>
</tr>
<tr>
<td>Time - LKW to EVT</td>
<td>125 min</td>
<td>137 min</td>
<td>0.12</td>
</tr>
</tbody>
</table>

--Audebert et al, ISC 2020
BEnefits of Stroke Treatment Delivered Using a Mobile Stroke Unit (BEST-MSU) Trial

• Cluster-control RCT
  » 5 EMS Regions USA
  » 1 week on, 1 week off
  » Patients
    • 6000 assessed
    • 1200 enrolled
      » 700 fully tPA eligible

• Key entry criteria
  » LKW within 4.5h prior to ambulance evaluation
  » tPA eligible prior to CT/labs

• Outcome: Utility-weighted mRS at 90d

• Timeline: 2014-2021
Catheter-Based Reperfusion Therapies
Mechanical Thrombectomy Devices

Coil Retriever
Stent Retriever
Covered Stent Retriever
Basket Retriever
Brush Retriever
Aspiration Catheter

UCLA Stroke Center
Acute Mechanical Recanalization Strategy Depends on Target Occlusion Composition

Emboli

- Relatively normal recipient artery
- Strategy: remove the thrombus
  - Retrievers
  - Aspirators
  - +/- Lytics

In Situ Atherothrombosis

- Substantial local atherosclerotic plaque
- Strategy: Crack the plaque
  - Angioplasty
  - Stents
  - +/- Lytics

UCLA Stroke Center
Determinants of Thrombectomy Success

- Clot burden
- Clot composition
- Clot tensile properties
- Tortuosity of feeding arteries
- Target artery size
- Recipient artery branching curvature
Should clot composition affect choice of endovascular therapy?

**ABSTRACT**

Endovascular therapy has become a promising alternative for patients who are ineligible for IV thrombolysis or for whom it has failed. Greater knowledge about the composition of thromboembolic material underlying the vascular occlusion in stroke patients may provide the means for improving existing endovascular therapies and developing new treatment strategies. The objective of this article is to provide a review of clinical and experimental animal studies on the histology, imaging correlation, and ultrastructure of thromboemboli retrieved during acute ischemic stroke. *Neurology* 2012;78 (Suppl 1):S63-S67

---

**Organized, Inelastic, Hard, Fibrin-Rich Clot**

- **Aspiration:**
  - Cohesive = lower risk of clot stripping/fragmentation during aspiration
  - **Stentriever:**
    - Inelastic so harder to be incorporated into the stent cells
    - **Push+Fluff Technique and/or larger or hybrid cells**

**Fresh, Elastic, Soft, RBC-Rich Clot**

- **Stentriever:**
  - Elastic = easier to be incorporated into the stent cells

- **Aspiration:**
  - Friable = higher risk of clot stripping/fragmentation during aspiration
  - Larger ID catheters closely matching vessel diameter

---

---Slide courtesy of R Nogueira---
UCLA – MCA Occlusion
30-Year-Old Female – Baseline NIHSS 24
Symptom Onset to Final Angiogram – 5:37

<table>
<thead>
<tr>
<th></th>
<th>NIHSS 24 hours</th>
<th>NIHSS 30 days post</th>
<th>mRS 5 days post</th>
<th>mRS 90 days post</th>
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<tr>
<td></td>
<td>1</td>
<td>0</td>
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</tbody>
</table>

NIHSS: National Institute of Health Stroke Scale
mRS: Modified Rankin Scale
Target: Stroke Phase 3

• Intravenous
  » Primary
    • DTN ≤ 60m in 85%
  » Secondary
    • DTN ≤ 45m in 75%
    • DTN ≤ 30m in 50%

• Endovascular
  » Door to Device (DTD)
    • EMS: DTD ≤ 90m in 50%
    • Tx: DTD ≤ 60m in 50%

*Door-to-device: arrival to first pass of thrombectomy device
1. Rapid alteplase start
2. Rapid CTA/MRA
3. Rapid additional imaging (6-24h)
4. Pre-Notification/Activation of Neurointerventional Team
5. Rapid availability of NI Team
6. Time attached to chart, clip board, or bed
7. In select patient, tx direct to neuroangio suite
8. Tx direct from brain imaging to angio suite
9. Team-based, parallel approach (ED, stroke, NI)
10. Endovascular-ready neuroangio suite
11. Anesthesia rapid protocols
12. Prompt data feedback
Progressors: Fast / Slow / Variable

DEFUSE 2

UCLA Series
--Liebeskind, 2016
Pathophysiology of Variation in Speed of Stroke Progression

- **Perfusion pressure**
  - Ejection fraction

- **Blood oxygenation**
  - Hemoglobin
  - Respiratory compromise

- **Collaterals**
  - Circle of Willis
  - Leptomeningeal
  - Deep

- **Tissue ischemic tolerance**
  - White vs gray matter
  - Excitatory vs inhibitory
  - Ischemic pre-conditioning

--Leemans, Neuro Bureau 2015
--Shuaib et al, Lancet Neurol 2011
--Bristow et al, JCBFM 2005
Bioenergetic Compromise

Hemodynamic Compromise

Occlusions or Stenoses
Strategies to Identify LVO Patients with Salvageable Ischemic Penumbra

- **< 6 Hrs**: Hyperacute therapy when nearly all patients have penumbra
- **> 6 Hrs**: Imaging required to assess pathophysiology
## Populations for Thrombectomy: Time and Penumbra

<table>
<thead>
<tr>
<th>Mismatch</th>
<th>0-3h</th>
<th>3-6h</th>
<th>6-7h</th>
<th>7-8h</th>
<th>8-12h</th>
<th>12-16h</th>
<th>16-20h</th>
<th>20-24h</th>
<th>&gt;24h</th>
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</thead>
<tbody>
<tr>
<td>Not performed</td>
<td>❌</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;200%</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>150-199%</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<td></td>
</tr>
<tr>
<td>100-149%</td>
<td>✔</td>
<td>✔</td>
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<td>✔</td>
<td>✔</td>
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<td></td>
</tr>
<tr>
<td>50-99%</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>20-49%</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
</tbody>
</table>
Regional Stroke Systems of Care
US Tier System

- **EMS** - recognize stroke and route to stroke centers

- **Spokes**
  - **Stroke Ready Hospitals (SRHs)**
    - Able to provide initial, ED care, often via telemedicine
    - Able to use tPA and other acute therapies safely and efficiently
  - **Primary Stroke Centers (PSCs)**
    - Able to provide initial, ED care
    - Able to use rt-PA and other acute therapies safely and efficiently
    - Have Stroke Units and can admit patient

- **Hubs**
  - **Thrombectomy Stroke Centers (TSCs)**
    - Able to provide endovascular thrombectomy but not other advanced care
  - **Comprehensive Stroke Centers (CSCs)**
    - Able to care for all complex patients
    - Advanced treatments (i.e., coils, clips, stents, endovascular recanalization, etc)
    - Key specialists

---

---Saver et al, Stroke Interventionalist 2013---
Identifying Likely Large Vessel Occlusion Patients in Field

- Medium (distal) vessel and small (penetrator) occlusions
  - IV tPA - works well, want asap
  - Thrombectomy – not an option
  - Primary Stroke Center or Acute Stroke Ready Hospital

- Large vessel occlusions
  - IV tPA - works poorly
  - Thrombectomy – works well
  - Comprehensive Stroke Center
Examples of Prehospital Stroke Scales to Identify LVO

- Los Angeles Motor Scale (LAMS)
  - 3 elements
  - Facial droop, arm drift, grip weakness

- 3 Item Stroke Scale (3I-SS)
  - 6 elements
  - Level of consciousness, gaze deviation, facial droop, arm drift, R/L leg weakness

- Rapid Arterial Occlusion Evaluation Score (RACE)
  - 7 elements
  - Facial droop, arm drift, R/L leg weakness, gaze deviation, aphasia, denial of hemiparesis

- Cincinnati Prehospital Stroke Severity Scale (CPSSS)
  - 4 elements
  - Gaze deviation, arm drift, LOC command, LOC questions

- Field Assessment Stroke Triage for Emergency Destination (Fast-ED)
  - 5 elements
  - Face, Arm weakness, speech, eye deviation, Denial/Neglect

- VAN
  - 3 elements
  - Vision, Aphasia, Neglect

Supported by NIH-NINDS
<table>
<thead>
<tr>
<th>LAMS</th>
<th>RACE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facial Droop</strong></td>
<td><strong>Facial Palsy</strong></td>
</tr>
<tr>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Present</td>
<td>Mild</td>
</tr>
<tr>
<td><strong>Arm Drift</strong></td>
<td><strong>Mod-severe</strong></td>
</tr>
<tr>
<td>Absent</td>
<td>Normal to mild</td>
</tr>
<tr>
<td>Drifts Down</td>
<td>Moderate</td>
</tr>
<tr>
<td>Falls Rapidly</td>
<td>Severe</td>
</tr>
<tr>
<td><strong>Grip Strength</strong></td>
<td><strong>Head + Gaze Dev</strong></td>
</tr>
<tr>
<td>Normal</td>
<td>Absent</td>
</tr>
<tr>
<td>Weak Grip</td>
<td>Present</td>
</tr>
<tr>
<td>No Grip</td>
<td><strong>Aphasia (if right HP)</strong></td>
</tr>
<tr>
<td></td>
<td>Normal to mild</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td><strong>Agnosia (if left HP)</strong></td>
</tr>
<tr>
<td></td>
<td>Normal to mild</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
</tr>
</tbody>
</table>
Optimal workflows all sites

- 90 min between thrombolysis and EVT center
- 120 min between thrombolysis and EVT center

Factors:
- Door to groin puncture
- Door to needle (thrombolysis center)
- Door to needle (EVT center)

Slow workflow at PSCs

- Patients beyond the blue line would not be able to receive adequate within 3.5 hours if they are transported to a remote endovascular therapy center.

Factors:
- Door to groin puncture
- Door to needle (thrombolysis center)
- Door to needle (EVT center)

---

Holodinsky et al, JAMA Neurol 2018
Los Angeles County
Two-Tier EMS Stroke Routing

• Population and Resources
  » 10.1 million individuals
  » 31 EMS agencies, 161 ambulances (1 MSU)
  » 50 designated stroke hospitals (~30 PSC, 5 TSC, 15 CSC)

• New routing policy - 2018
  » If suspected stroke (mLAPSS positive)
  » Direct to nearest CSC or TSC, if
    » ≥ 4, likely LVO if ACI, AND,
    » Last known well is within 24h, AND
    » TSC or CSC is within 30 mins
  » Otherwise, direct to PSC
    • Accelerated inter-facility transfer if needed

UCLA Stroke Center
Initial Impact of Two-Tiered Routing in a Major Metropolitan Region (LA)

UCLA Stroke Center

Access to Endovascular Treatment within a 30 minute transport:

40% → 93%

ODDS RATIOS FOR OUTCOMES

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPA Administration</td>
<td>23.4%</td>
<td>26.6%</td>
</tr>
<tr>
<td></td>
<td>OR 1.2, 95% CI 1.03-1.4</td>
<td></td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>5.2%</td>
<td>13.5%</td>
</tr>
<tr>
<td></td>
<td>OR 2.8, 95% CI 2.3-3.8</td>
<td></td>
</tr>
<tr>
<td>Inter-facility Transfer</td>
<td>3.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td></td>
<td>OR 0.3, 95% CI 0.2-0.5</td>
<td></td>
</tr>
</tbody>
</table>

--Bosson et al, Stroke 2020
Stroke physician prehospital real-time telestroke assessment of the National Institutes of Health Stroke Scale in the moving ambulance

Liman T G et al. Stroke 2012;43:2086-2090

Copyright © American Heart Association

Figure 1 iTREAT ambulance setup with cradled iPad and suction mounting
Stroke Helmets: Biometric Devices

- **Radiofrequency**
  - Cerebrotech Visor
    - Cerebrotech
  - SENSE
    - Sense Neuro

- **EEG**
  - AlphaStroke
    - ForestDevices
  - EDSAP
    - Samsung

- **Ultrasound**
  - NovaGuide Robotic
    - NovaSignal
  - SONAS
    - Burl

- **Near infra-red**
  - EQUANOX
    - Nonin Medical

- **Cranial accelemytery**
  - Mindrhythm Harmony
    - Mindrhythm

- **Microwave**
  - Strokefinder
    - Medfield

*UCLA Stroke Center*
COVID-19 and Acute Stroke

UCLA Stroke Center
General Features of COVID-19 Patients with Stroke

- 2-3% of all COVID-19 admits
- Median age 70-75
- More severe COVID-19 disease
- More RFs of HTN, DM, CAD, prior stroke
- Average time of stroke onset after COVID dx – 12 days

Table 1: Baseline characteristics of COVID-19 patients with new onset of CVD during infection

<table>
<thead>
<tr>
<th>Type of CVD</th>
<th>Subtype of CVD</th>
<th>Age, y</th>
<th>Sex</th>
<th>Smoking History</th>
<th>Drinking History</th>
<th>Blood pressure (mm Hg)</th>
<th>Fasting Blood glucose (mmol/L)</th>
<th>Type of COVID-19</th>
<th>Onset Time of SARS-CoV-2 Infection (h)</th>
<th>Onset Time of CVD (h)</th>
<th>Treatment of CVD</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AIS</td>
<td>79</td>
<td>M</td>
<td>Yes</td>
<td>No</td>
<td>103/70</td>
<td>5.44</td>
<td>Severe</td>
<td>04/06/20</td>
<td>02:30</td>
<td>Anticoagulant</td>
<td>Survival</td>
</tr>
<tr>
<td>2</td>
<td>AIS</td>
<td>72</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td>120/87</td>
<td>6.03</td>
<td>Severe</td>
<td>04/08/20</td>
<td>02:00</td>
<td>Anticoagulant</td>
<td>Survival</td>
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<td>3</td>
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<td>80</td>
<td>F</td>
<td>Yes</td>
<td>No</td>
<td>101/97</td>
<td>6.77</td>
<td>Severe</td>
<td>04/10/20</td>
<td>02:30</td>
<td>Anticoagulant</td>
<td>Survival</td>
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<tr>
<td>4</td>
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<td>71</td>
<td>F</td>
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<td>No</td>
<td>100/87</td>
<td>6.7</td>
<td>Severe</td>
<td>04/10/20</td>
<td>03:00</td>
<td>Anticoagulant</td>
<td>Survival</td>
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<td>5</td>
<td>AIS</td>
<td>72</td>
<td>F</td>
<td>No</td>
<td>No</td>
<td>101/89</td>
<td>7.93</td>
<td>Severe</td>
<td>04/10/20</td>
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<td>Anticoagulant</td>
<td>Survival</td>
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<tr>
<td>6</td>
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<td>76</td>
<td>M</td>
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<tr>
<td>7</td>
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<td>74</td>
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<td>No</td>
<td>105/72</td>
<td>7.99</td>
<td>Severe</td>
<td>04/10/20</td>
<td>04:00</td>
<td>Anticoagulant</td>
<td>Survival</td>
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<tr>
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<td>Yes</td>
<td>No</td>
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<td>Severe</td>
<td>04/10/20</td>
<td>04:00</td>
<td>Anticoagulant</td>
<td>Survival</td>
</tr>
<tr>
<td>9</td>
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<td>76</td>
<td>M</td>
<td>Yes</td>
<td>No</td>
<td>101/83</td>
<td>11.11</td>
<td>Severe</td>
<td>04/10/20</td>
<td>04:00</td>
<td>Anticoagulant</td>
<td>Survival</td>
</tr>
<tr>
<td>10</td>
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<td>77</td>
<td>M</td>
<td>Yes</td>
<td>No</td>
<td>127/83</td>
<td>13.94</td>
<td>Severe</td>
<td>04/10/20</td>
<td>04:00</td>
<td>Anticoagulant</td>
<td>Survival</td>
</tr>
<tr>
<td>11</td>
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<td>69</td>
<td>F</td>
<td>Yes</td>
<td>No</td>
<td>98/62</td>
<td>8.47</td>
<td>Severe</td>
<td>04/10/20</td>
<td>05:00</td>
<td>Anticoagulant</td>
<td>Survival</td>
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<tr>
<td>12</td>
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<td>M</td>
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<td>Yes</td>
<td>130/80</td>
<td>8.23</td>
<td>Severe</td>
<td>04/10/20</td>
<td>06:00</td>
<td>Anticoagulant</td>
<td>Survival</td>
</tr>
</tbody>
</table>

*The patients of COVID-19 were confirmed by SARS-CoV-2 RT-PCR positive in throat swab and visible pneumonia in chest CT. Abbreviations: COVID-19, Coronavirus disease 2019; CVD, Cardiovascular disease; AIS, Acute ischemic stroke; CH, Cerebral hemorrhage; CVST, Cerebral Venous Sinus Thrombosis; E, Female; M, Male.

Mechanisms Contributing to COVID-19 Related Stroke

- All the usual stroke mechanisms, plus
- Activated inflammatory state and coagulation cascade
  - Elevated CRT and d-dimer
  - Time-based clot waveform analysis shows hypercoagulability precedes or coincides with severe illness
  - Autopsy findings in COVID-19 suggest thrombotic microangiopathy in multiple organs especially lungs
  - --> Hypercoagulability leading to macro and micro thrombi formation in the vessels
- Antiphospholipid Ab syndrome
- Vasculitis
- Paradoxical embolism
- Cerebral venous thrombosis

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--Expanded from Avula et al, Brain, Behav, Immun 2020
--Kansagra et al, NEJM 2020

- Penumbra imaging automated post-processing software
  » RAPID software platform (iSchemaView)
- 856 US hospitals
- 231,753 acute patients
  » 7/1/19 – 4/27/20
Altered Care Pathways During COVID-19 Pandemic

• Less frequent MRI (longer decontamination)
• Less frequent TEE (aerosolized exposures)
• Less frequent/no transfers at peak
• Triage at extreme peak

--Qureshi A, et al. AJEM 2020

RRMC-UCLA Comprehensive Stroke Center
Single stroke neurologist provides immediate expertise to multiple EDs, ICUs, ambulances.

Videocart
Telemedicine

Videorobot
Telepresence

Videocell phone
Tele-omnipresence
IV Tenecteplase vs Alteplase in AIS: Post-COVID More Advantages

- **Alteplase**
  - 60m infusion
    - Multiple infusion pump checks
    - Increased PPE consumption
    - Increased infection risk
  - Supplies exhausted in some countries
    - Case series suggesting alteplase may be beneficial for averting diffuse pulmonary thrombosis in COVID-19
    - General supply chain disruption

- **Teneteplase**
  - 1m bolus
    - Reduced PPE consumption
    - Reduced infection risk
  - Supplies good in most countries

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--Warach + Saver, JAMA Neurol, 2020