Stroke Update: New Tricks for an Old Dogma

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Presenter Disclosure Information

Patrick D. Lyden
New Tricks for an Old Dogma

NINDS R01 NS075930 (PI)
NINDS U01 NS088312 (PI)
NINDS U24 NS113452 (PI)

FINANCIAL DISCLOSURE:
I have no relationship with any company associated with thrombolysis or thrombectomy

UNLABELED/UNAPPROVED USES DISCLOSURE:
I will describe uses of a number of drugs based on dogma and very little science.
CBF in pathological states

Graph showing the relationship between CBF (mL/min/100 g) and PaCO$_2$ (mmHg). The graph illustrates impaired autoregulation and preserved autoregulation regions.
Strandgaard et al
Autoregulation of Brain Circulation in Severe Arterial Hypertension
Baseline

After Occlusion

Where's the data?
That occlusion will never open

Stroke. 2016;47:2409–2412
Intimal hyperplasia
Fibrinoid or cystic medial necrosis
Long, penetrating arteries

C.M. Fisher
"The Arterial Lesions Underlying Lacunes"
Acta neuropath. (Berlin) 12, 1-15, 1969

Acta neuropath. (Berlin) 12, 1-15, 1969
Thrombectomy
IA STUDY POPULATION

Time from Onset

- 12h
- 6h
- 2h

tPA Tx

Unlikely

Likely

All ICA or M1 MCA Occlusions

ESCAPE

EXTEND IA

SWIFT PRIME

MR CLEAN

low ASPECTS
- poor collaterals
- large core

good ASPECTS
- good collaterals
- small core

ALL SHOWED BENEFIT OF ENDOVASCULAR TREATMENT

Slide credit: M. Goyal ESCAPE Trial Presentation
**Meta-analysis**


---

**B**

**Ineligible for alteplase**

- **Control population** (n=80)
  - 3.6
  - 6.2
  - 12.5
  - 8.7
  - 31.2
  - 15.0
  - 22.5

- **Intervention population** (n=108)
  - 10.2
  - 15.7
  - 17.6
  - 18.5
  - 7.4
  - 7.4
  - 23.1

**Received alteplase**

- **Control population** (n=565)
  - 5.1
  - 8.1
  - 13.8
  - 17.5
  - 23.7
  - 13.3
  - 18.4

- **Intervention population** (n=525)
  - 9.9
  - 17.1
  - 19.4
  - 16.6
  - 17.3
  - 5.9
  - 13.7
## Table 4: Safety outcomes at 90 days

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention population</th>
<th>Control population</th>
<th>Adjusted rate ratio (95% CI)</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic intracranial haemorrhage</td>
<td>4.4% (28/634)</td>
<td>4.3% (28/653)</td>
<td>1.07 (0.62–1.80); p=0.81</td>
<td>1.07 (0.62–1.84); p=0.81</td>
</tr>
<tr>
<td>Parenchymal haematoma type 2</td>
<td>5.1% (32/629)</td>
<td>5.3% (34/641)</td>
<td>1.04 (0.64–1.69); p=0.88</td>
<td>1.04 (0.63–1.72); p=0.88</td>
</tr>
<tr>
<td>Mortality</td>
<td>15.3% (97/633)</td>
<td>18.9% (122/646)</td>
<td>0.82 (0.62–1.08); p=0.15</td>
<td>0.73 (0.47–1.13); p=0.16</td>
</tr>
</tbody>
</table>

Data show the proportion of patients with outcome (n/N), unless otherwise specified.
A  Intention-to-Treat Population

Thrombectomy (N=107)

Control (N=99)

Score on the Modified Rankin Scale

- 0
- 1
- 2
- 3
- 4
- 5 or 6

Percent of Patients

6-24 hours LKNW
DEFFUSE-3
Albers et al. NEJM 2018; 378:708-18

Volume of Ischemic Core, 23 ml
Volume of Perfusion Lesion, 128 ml

Mismatch volume, 105 ml
Mismatch ratio, 5.6
DEFFUSE-3
Albers et al. NEJM 2018; 378:708-18

Department of Neurology
Novel Oral Anticoagulants
The diagram illustrates the coagulation cascade and platelet aggregation, starting from injured endothelium or blood stasis. The intrinsic pathway begins with Factor XII (XII) activating Factor XIIa (XIIa), which in turn activates Factor XI (XI) to Factor XIa (IXa), followed by Factor IX (IX) activating Factor VIII (VIII) to Factor VIIIa (VIIIa), and Factor VIIIa activating Factor X (X) to Factor Xa (Xa). Factor Xa then activates Factor Va (Va) to Factor Va (Va), leading to the formation of Factor IIa (IIa) and ultimately Factor Ia (Ia), which promotes clot formation. Platelet aggregation is a key process in this cascade. The extrinsic pathway begins with Factor VII (VII) activating Factor VIIa (VIIa), which then activates Factor X (X). The diagram also shows the role of thrombin (IIa) in converting plasminogen to plasmin, aiding in clot dissolution. Direct factor Xa inhibitors include apixaban, rivaroxaban, and direct thrombin inhibitors such as dabigatran.
Dabigatran: Re-LY

NEJM 2009; 361:2342-52
Apixaban: AVERROES

**Hazard ratio with apixaban, 0.45 (95% CI, 0.32–0.62)**

P < 0.001

**Cumulative Hazard**

**Months**

NEJM 2011;364:806-17
Rocket AF

A Events in Per-Protocol Population

No. at Risk
Rivaroxaban 6958 6211 5786 5468 4406 3407 2472 1496
Warfarin 7004 6327 5911 5542 4461 3478 2539 1538

NEJM 2011; 365:883-891
### Effects of Non–Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: A Systematic Review and Meta-Analysis

#### Table: Hazard Ratio Summary

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.1.1 Stroke or systemic embolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE⁹</td>
<td>0.29266961</td>
<td>0.08925584</td>
<td>25.9%</td>
<td>1.34 [1.12, 1.60]</td>
</tr>
<tr>
<td>ENGAGE AF¹³</td>
<td>-0.0618754</td>
<td>0.0876787</td>
<td>26.2%</td>
<td>0.94 [0.79, 1.12]</td>
</tr>
<tr>
<td>RELY¹⁰</td>
<td>0.0861777</td>
<td>0.09455796</td>
<td>24.9%</td>
<td>1.09 [0.91, 1.31]</td>
</tr>
<tr>
<td>ROCKET AF¹¹</td>
<td>0.06765865</td>
<td>0.10448695</td>
<td>23.0%</td>
<td>1.07 [0.87, 1.31]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>1.10 [0.95, 1.28]</td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> Tau² = 0.02; Chi² = 8.18, df = 3 (P = 0.04); I² = 63%</td>
<td></td>
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</tr>
<tr>
<td><strong>Test for overall effect:</strong> Z = 1.25 (P = 0.21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **3.1.2 All-cause mortality** | | | | |
| ARISTOTLE⁹ | 0.39204209 | 0.05647828 | 25.4% | 1.48 [1.32, 1.65] |
| ENGAGE AF¹³ | 0.33647224 | 0.05157965 | 25.9% | 1.40 [1.27, 1.55] |
| RELY¹⁰ | 0.0861777 | 0.05931623 | 25.1% | 1.09 [0.97, 1.22] |
| ROCKET AF¹¹ | 0.0861777 | 0.0716109 | 23.6% | 1.09 [0.95, 1.25] |
| **Subtotal (95% CI)** | | | | 1.26 [1.07, 1.47] |
| **Heterogeneity:** Tau² = 0.02; Chi² = 22.00, df = 3 (P < 0.0001); I² = 86% | | | | |
| **Test for overall effect:** Z = 2.86 (P = 0.004) | | | | |

| **3.1.3 Major bleeding** | | | | |
| ARISTOTLE⁹ | 0.10436002 | 0.07209874 | 25.0% | 1.11 [0.96, 1.28] |
| ENGAGE AF¹³ | 0.19062036 | 0.07536532 | 23.4% | 1.21 [1.04, 1.40] |
| RELY¹⁰ | 0.27763174 | 0.06137049 | 31.3% | 1.32 [1.17, 1.49] |
| ROCKET AF¹¹ | 0.27763174 | 0.0827267 | 20.3% | 1.32 [1.12, 1.55] |
| **Subtotal (95% CI)** | | | | 1.24 [1.14, 1.34] |
| **Heterogeneity:** Tau² = 0.00; Chi² = 4.07, df = 3 (P = 0.25); I² = 26% | | | | |
| **Test for overall effect:** Z = 5.09 (P < 0.00001) | | | | |

| **3.1.4 Intracranial hemorrhage** | | | | |
| ENGAGE AF¹³ | -0.040822 | 0.16603184 | 32.9% | 0.96 [0.69, 1.33] |
| RELY¹⁰ | 0.18232156 | 0.15465632 | 37.7% | 1.20 [0.89, 1.62] |
| ROCKET AF¹¹ | 0.30010459 | 0.1768264 | 29.4% | 1.35 [0.96, 1.91] |
| **Subtotal (95% CI)** | | | | 1.15 [0.95, 1.40] |
| **Heterogeneity:** Tau² = 0.00; Chi² = 2.09, df = 2 (P = 0.35); I² = 4% | | | | |
| **Test for overall effect:** Z = 1.48 (P = 0.14) | | | | |

**Test for subgroup differences:** Chi² = 2.25 df = 3 (P = 0.52) I² = 0%
Thrombin toxicity
Thrombin toxicity
Thrombin toxicity

Ischemia

Thrombin Activation

Intravascular

Coagulation Cascade

Microthrombosis

Vascular and Tissue Injury
<table>
<thead>
<tr>
<th>Trial</th>
<th>Interval</th>
<th>Agent</th>
<th>Patients Treated, N</th>
<th>Dead, n (%)</th>
<th>Poor, n (%)</th>
<th>Good, n (%)</th>
<th>Excellent, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISS</td>
<td>6 mo</td>
<td>HD nadroparin</td>
<td>102</td>
<td>13 (12.7)</td>
<td>32 (31.3)</td>
<td>...</td>
<td>57 (55.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LD nadroparin</td>
<td>101</td>
<td>17 (16.8)</td>
<td>36 (35.6)</td>
<td>...</td>
<td>48 (47.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>105</td>
<td>20 (19.0)</td>
<td>...</td>
<td>...</td>
<td>37 (35.2)</td>
</tr>
<tr>
<td>IST</td>
<td>6 mo</td>
<td>HD heparin</td>
<td>4856</td>
<td>1103 (22.7)</td>
<td>1389 (28.3)</td>
<td>612 (12.7)</td>
<td>824 (17.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LD heparin</td>
<td>4860</td>
<td>1237 (25.4)</td>
<td>1557 (32.0)</td>
<td>373 (7.6)</td>
<td>831 (17.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>9718</td>
<td>1777 (18.3)</td>
<td>3758 (38.8)</td>
<td>2183 (22.4)</td>
<td>1641 (17.0)</td>
</tr>
<tr>
<td>TOAST</td>
<td>3 mo</td>
<td>Danaparoid</td>
<td>1234</td>
<td>20 (1.7)</td>
<td>77 (6.3)</td>
<td>42 (3.4)</td>
<td>317 (25.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>1350</td>
<td>25 (1.9)</td>
<td>75 (5.6)</td>
<td>...</td>
<td>298 (22.1)</td>
</tr>
<tr>
<td>HAEST</td>
<td>3 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAIST</td>
<td>6 mo</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FISS-bis</td>
<td>6 mo</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>TOPAS</td>
<td>3 mo</td>
<td>Certoparin 3000/d</td>
<td>96</td>
<td>59 (61.5)</td>
<td>37 (38.5)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Certoparin 3000 BID</td>
<td>97</td>
<td>59 (60.8)</td>
<td>38 (39.2)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Certoparin 5000 BID</td>
<td>98</td>
<td>62 (63.3)</td>
<td>36 (36.7)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Certoparin 8000 BID</td>
<td>96</td>
<td>54 (56.3)</td>
<td>42 (43.7)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Favorable, n (%)

See Table 1 for doses of medication prescribed to HD and LD groups.
Thrombin toxicity

- Ischemia
  - Thrombin Activation
    - Intravascular
      - Coagulation Cascade
        - Microthrombosis
    - Neurovascular
      - PAR-1 Activation
        - Cytotoxicity
      - Vascular and Tissue Injury
Neuronal Labeling of Thrombin

FITC-dextran
Cy3-α-NeuN
Cy5-α-thrombin

Mechanism of PAR-1 Activation

(Coughlin SR, 2005)
NeuroNEXT NN104 (RHAPSODY) Study

Results and Close-Out Meeting

January 22nd, 2018
Confirmed Randomizations

N = 110

3K3A-APC

N = 66

- 120 μg/kg
  N = 15

- 240 μg/kg
  N = 24

- 360 μg/kg
  N = 12

- 540 μg/kg
  N = 15

Placebo

N = 44

Randomized Subjects

N = 120 μg/kg

N = 240 μg/kg

N = 360 μg/kg

N = 540 μg/kg
## Hemorrhage

<table>
<thead>
<tr>
<th>Hemorrhage Type at Day 30</th>
<th>Total</th>
<th>Dose</th>
<th>p-value (3K3A-APC vs. PBO)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>120 (N=12)</td>
<td>240 (N=16)</td>
</tr>
<tr>
<td>Hemorrhage (&gt;0 mL)</td>
<td>61 (76.3%)</td>
<td>8 (66.7%)</td>
<td>13 (81.3%)</td>
</tr>
<tr>
<td>(&gt;0.06 mL)</td>
<td>49 (61.3%)</td>
<td>7 (58.3%)</td>
<td>11 (68.8%)</td>
</tr>
<tr>
<td>(&gt;0.5 mL)</td>
<td>24 (30.0%)</td>
<td>4 (33.3%)</td>
<td>5 (31.3%)</td>
</tr>
<tr>
<td>(&gt;1.8 mL)</td>
<td>13 (16.3%)</td>
<td>1 (8.3%)</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Microbleeds</td>
<td>15 (18.8%)</td>
<td>1 (8.3%)</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Total Hemorrhage Volume</td>
<td>0.8±2.1</td>
<td>2.1±5.8</td>
<td></td>
</tr>
</tbody>
</table>
## Hemorrhage

<table>
<thead>
<tr>
<th>Hemorrhage Type at Day 30</th>
<th>Total</th>
<th>Dose</th>
<th>All 3K3A-APC (N=43)</th>
<th>Placebo (N=37)</th>
<th>p-value (3K3A-APC vs. PBO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage (&gt;0 mL)</td>
<td>61 (76.3%)</td>
<td>120 (N=12)</td>
<td>8 (66.7%)</td>
<td>29 (67.4%)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>240 (N=16)</td>
<td>13 (81.3%)</td>
<td>32 (86.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>360 (N=6)</td>
<td>3 (50.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>540 (N=9)</td>
<td>5 (55.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>(&gt;1.8 mL)</td>
<td>13 (16.3%)</td>
<td>120 (N=12)</td>
<td>1 (8.3%)</td>
<td>1 (9.3%)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>240 (N=16)</td>
<td>2 (12.5%)</td>
<td>4 (9.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>360 (N=6)</td>
<td>0 (0.0%)</td>
<td>1 (11.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>540 (N=9)</td>
<td>1 (11.1%)</td>
<td>9 (24.3%)</td>
<td></td>
</tr>
<tr>
<td>Total Hemorrhage Volume</td>
<td></td>
<td></td>
<td>0.8±2.1</td>
<td>2.1±5.8</td>
<td>0.07</td>
</tr>
</tbody>
</table>
tPA plus Argatroban 100mcg/kg
Target PTT 1.75x
sICH in 3 (4.6%)
Early recanalization In 61%
To be tested in upcoming MOST trial
“Truth does not change because it is, or is not, believed by a majority of the people.”
Thank you
New Uses for Transcranial Doppler Monitoring
Intracranial Emboli Detection
New Indications

- Detection of Patent Foramen Ovale
- Emboli Detection
- Intra-operative monitoring
High Intensity Transients (HIT)
Detection of PFO

• **TCD superior to TTE with bubbles**
  - Sensitivity 68% vs 47%
  - Di Tullio, Sacco et al. Stroke 1993;24:1020-1024

• **Contrast TCD superior to contrast TEE**
  - Sensitivity 75% vs 48% without Valsalva
  - Both 100% with Valsalva

• All 3 are somewhat operator dependent
25 patient studies
8 positive for PFO
Of those 8, 2 were NEGATIVE on TTE
All confirmed on angio
Emboli Detection
Risk of stroke with Asymptomatic Carotid Stenosis

Figure 2 Kaplan-Meier survival by baseline status

[Graph showing Kaplan-Meier survival curves for stroke/death/TIA (proportion) over days with different baseline statuses and ultrasound findings.]
Risk of stroke with Symptomatic Carotid Stenosis

B

Survival free of ipsilateral stroke or TIA

Time (days)

embolic signals

- emboli detected
  - censored
- no emboli
  + no emboli-censored

Department of Neurology  Stroke. 2005; 36: 971-975
Transcranial Doppler Microembolic Signal Monitoring is Useful in Diagnosis and Treatment of Carotid Artery Dissection: Two Case Reports
Case

• 61 yo former pro bass fisherman
• Several episodes dizzy, diplopia, all resolved
• Most recent spell treated in ED with nitro paste and benadryl
• PMD treated with steroids
• 3 days later returned to ED with same sx
  ○ CT scan showed bilateral cerebellar strokes
• Referred to Cedars-Sinai urgently
More history…

• 3 months prior was seen for acute stroke: vertigo and hemi-body numbness
• Transferred to a tertiary facility
• Added asa to his plavix
• CTA said to show occluded left vertebral artery
Initial TCD

30 HITS right PCA, none in the left

Department of Neurology
Titrate anti-thrombotic therapy

- Since he was having HITS on ASA and Plavix we changed to prasugrel
- TCD one week later showed 9 HITS so we added aggrenox
- One month later, no sx but repeat TCD “artifact laden”
- Two months later, repeat TCD: no HITS
- One year after initial strokes, no HITS so we stopped aggrenox
- Two years after stroke, still has occluded vert and low basilar flow:
- No strokes
Titrate anti-thrombotic therapy

**BASILAR**

12:21:24 PM

- Depth: 94
- Power: 100
- Sample: 9
- Peak: -25*
- Dias: -9*
- Mean: -15*
- P.l.: 1.04*
Thank You