Correlating Lab Tests and the Why’s Behind Them

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Outline

• Emergency labs

• Admit labs – risk stratification
  • Hypercoagulable state testing
  • Vasculitis
  • Genetic testing for stroke

• Emerging labs
  – Platelet function assays
  – NT-proBNP
Emergency labs - Creatinine

- Meta-analysis showed that AKI rate not higher in acute stroke patients that got CTA/CTP
- DO NOT have to wait for creatinine to do this contrast based imaging

Stroke. 2017;48: 1862-1868
Emergency labs
Emergency Stroke Panel

• At HMC/UWMC we do an Emergency Stroke Panel or “ESP” – median turn around **14 minutes**
• To rule out coagulopathy in preparation for ?tPA or as explanation for hemorrhage...
• Includes:
  – Complete Blood Count (CBC)
    • Hemoglobin, hematocrit, platelets
  – Prothrombin Time (PT)
  – International Normalized Ratio (INR)
  – Partial thrombin time (PTT)
  – Thrombin Time (TT)
  – Anti-Xa levels
  – Fibrinogen
CBC, Hb/Hct

• Hemoglobin (Hb)/hematocrit (Hct)
  – Measure of red blood cell mass
  – The Hct can be measured directly by centrifuging a tube of whole blood. The ratio of the packed red cell column height to the total height is the Hct. Note that the Hct is a unitless value (a percentage)
  – Rule out significant anemia
  – If low, suggests possible “active internal bleeding” which is a tPA contraindication
CBC, platelets

- Platelet count is a key marker of a hemorrhagic tendency
- <100,000 tPA contraindication for tPA
- If very low with hemorrhage, may need platelet transfusion
- If platelet count >100k, would **NOT** transfuse platelets for ICH on antiplatelet medications
Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial


- >90% on aspirin +/- other antiplatelet med
- Within 6 hrs of supratentorial ICH
- Platelet transfusion within 90 min
- N=190, median NIHSS=13, median GCS=14
- Median ICH score=1 (low)
- Median ICH volume~10cc (smaller)

**Figure 2: Distribution of mRS score at 3 months**

mRS=modified Rankin Scale. OR=odds ratio.

<table>
<thead>
<tr>
<th></th>
<th>Platelet transfusion group (n=97)</th>
<th>Standard care group (n=93)</th>
<th>Odds ratio (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive at 3 months (survival)</td>
<td>66 (68%)</td>
<td>72 (77%)</td>
<td>0·62 (0·33–1·19)</td>
<td>0·15</td>
</tr>
<tr>
<td>mRS score 4–6 at 3 months</td>
<td>70 (72%)</td>
<td>52 (56%)</td>
<td>2·04 (1·12–3·74)</td>
<td>0·0195</td>
</tr>
<tr>
<td>mRS score 3–6 at 3 months</td>
<td>86 (89%)</td>
<td>76 (82%)</td>
<td>1·75 (0·77–3·97)</td>
<td>0·18</td>
</tr>
<tr>
<td>Median ICH growth at 24 h (mL)*</td>
<td>2·01 (0·32–9·34)</td>
<td>1·16 (0·03–4·42)</td>
<td></td>
<td>0·81</td>
</tr>
</tbody>
</table>

Data are n (%) or median (IQR). mRS=modified Rankin Scale. ICH=intracerebral haemorrhage. *n=80 in platelet transfusion group and 73 in standard care group.

**Table 2: Secondary outcomes in the intention-to-treat population**
Coags
PT
INR
PTT
TT

Extrinsic

Intrinsic

Common

https://bloggingforyournoggin.wordpress.com/2016/04/05/the-clotting-cascade-made-easy/
## Antithrombotics (thrombolytics, anticoagulants and antiplatelet drugs) (B01)

<table>
<thead>
<tr>
<th><strong>Anticoagulants</strong></th>
<th><strong>Factor Xa inhibitors (with some II inhibition)</strong></th>
<th><strong>Heparin group/glycosaminoglycans (bind antithrombin)</strong></th>
<th><strong>Direct Xa inhibitors (&quot;xabans&quot;)</strong></th>
<th><strong>Direct thrombin (IIa) inhibitors</strong></th>
<th><strong>Other</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K antagonists (inhibit II, VII, IX, X)</td>
<td>Coumarins: Acenocoumarol · Coumatetralyl · Dicoumarol · Ethyl biscoumacetate · Phenprocoumon · Warfarin† · 1,3-Indandiones: Clorindione · Diphenadione · Phenindione · Other: Tioctamarol</td>
<td>Low molecular weight heparin (Bemiparin · Certoparin · Dalteparin · Enoxaparin · Nadroparin · Parnaparin · Reviparin · Tinzaparin) · Oligosaccharides (Fondaparinux · Idraparinux§) · Heparinoids (Danaparoid · Dermatan sulfate · Sulodexide)</td>
<td>Apixaban · Betrixaban · Daretaban§ · Edoxaban · Otamixaban§ · Rivaroxaban</td>
<td>Bivalent: Hirudin (Bivalirudin · Desirudin · Lepirudin) · Univalent: Argatroban · Dabigatran · Efragatan · Inogatran§ · Melagatran‡ · Ximelagatran‡</td>
<td>Antithrombin III · Defibrotide · Protein C (Drotrecogin alfa†) · Ramatroban · REG1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Antiplatelet drugs</strong></th>
<th><strong>Glycoprotein IIb/IIIa inhibitors</strong></th>
<th><strong>ADP receptor/P2Y12 inhibitors</strong></th>
<th><strong>Prostaglandin analogue (PGI2)</strong></th>
<th><strong>COX inhibitors</strong></th>
<th><strong>Thromboxane inhibitors</strong></th>
<th><strong>Phosphodiesterase inhibitors</strong></th>
<th><strong>Other</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abciximab · Eptifibatide · Orbofiban · Roxifiban · Sibrafiban§ · Tirofiban</td>
<td>Thienopyridines (Clopigregrel · Prasugrel · Ticlopidine) · Nucleotide/nucleoside analogs (Cangrelor · Elinogrel · Ticagrelor)</td>
<td>Beraprost · Iloprost · Prostacyclin · Treprostinil</td>
<td>Acetylsalicylic acid/Aspirin‡ · Aloxiprin · Carbasalate calcium · Indobufen · Trifusale</td>
<td>Thromboxane synthase inhibitors (Dipyridamole (+ aspirin) · Picotamide · Terbogrel) · Receptor antagonists (Terbogrel · Terutroban§)</td>
<td>Cilostazol · Dipyridamole · Trifusale</td>
<td>Cloricromen · Ditizele · Vorapaxar</td>
</tr>
</tbody>
</table>

| **Thrombolytic drugs/fibrinolytics** | Plasminogen activators: r-tPA (Alteplase · Retapase · Tenecteplase · Desmoteplase†) · UPA (Saruplase · Urokinase) · Anistreplase · Montepase · Streptokinase§ · Other serine endopeptidases: Ancrod · Brinase · Fibrinolysin | Citrate · EDTA · Oxalate | | | |

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#WHO-EM · †Withdrawn from market · Clinical trials: (†Phase III · §Never to phase III)
Coags – PT/INR, PTT, TT

• PT/INR (Prothrombin Time/International Normalized Ratio)
  – Measures coagulation factors in the extrinsic and common pathways (factors I (Fibrinogen), II (Prothrombin), V, VII and X)
  – Indicator of warfarin anticoagulation
  – INR standardizes across labs
• PTT (Partial Thromboplastin Time)
  – Measures clotting factors of the intrinsic and common pathways (XII, XI, IX, VIII, X, V, II (prothrombin), and I (fibrinogen))
  – Indicator of unfractionated heparin anticoagulation
  – Can be abnormal with a lupus anticoagulant
• TT (Thrombin Time)
  – Assesses activity of fibrinogen
  – Indicator of dabigatran or heparin anticoagulation

https://labtestsonline.org
Anti-Xa levels, Fibrinogen

• Anti-Xa levels
  – Measures extent of inhibition of exogenous FXa
  – Indicator of UFH, LMWH, anti-Xa anticoagulation
    • Xa inhibitors include apixaban, endoxaban, rivaroxaban

• Fibrinogen
  – Measures amount/activity levels
  – Low suggests higher risk of bleeding
  – High in many conditions, including stroke, as is an “acute phase reactant”
    • may rise sharply in any condition that causes inflammation or tissue damage

https://labtestsonline.org
Warfarin
Unfractionated Heparin
Direct Thrombin Inhibitors

- Dabigatran
- Bivalirudin
- Argatroban

https://step1.medbullets.com/hematology/111030/anticoagulants
Factor Xa Inhibitors
LMWH, Fondaparinux
Rivaroxaban
Apixaban
Endoxaban

https://step1.medbullets.com/hematology/111030/anticoagulants
Admit Labs – risk stratification

• Diabetes
  – Glucose levels (actually emergency test)
    • Very low or high can mimic stroke, need for tPA
    • NEW data on inpatient post stroke management
  – Hemoglobin A1c: evaluates the average amount of glucose in the blood over last 2 to 3 months by measuring % of glycated hemoglobin
    • Normal: < 5.7% (39 mmol/mol)
    • Diabetes: ≥ 6.5% (48 mmol/mol)
    • Borderline/pre-diabetes: 5.7-6.4% (39-46 mmol/mol)
    • Important to optimize secondary prevention

https://labtestsonline.org
SHINE Trial – Presented at ISC 2019

Intensive vs. Standard Treatment of Hyperglycemia in AIS

- NIH funded, RCT, N=1151 at 70 US centers
- Known T2DM (BG>110) or BG>150
- NIHSS 3-22
- Treatments (within 12 hours thru 72 hours)
  - Intensive: Insulin drip – target 80-130 mg/dL
  - Standard: SQ insulin q6 hr – target <180 mg/dL
- Results: intensive NOT better, more hypoglycemia
Admit Labs – risk stratification

• Cholesterol/Lipid Panel
  – Important to optimize secondary prevention
  – 2018 ACC/AHA Cholesterol Guidelines
    • Check to establish LDL if not on Rx
    • High intensity statin in stroke with atherosclerosis
    • Lower level of evidence regarding adding other medications

https://labtestsonline.org
https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625
Hypercoagulable State Labs

• Arterial
  – Antiphospholipid antibodies
  – Homocysteine: low evidence, Rx unclear, genetic SVS?

• Venous (only if PFO or other R→L shunt?)
  – Factor V Leiden mutation
  – Prothrombin (Factor II) gene mutation
  – Protein C deficiency
  – Protein S deficiency
  – Antithrombin III deficiency
  – Factor VIII elevations?
Hypercoagulable State Factors

Contact activation (intrinsic) pathway

Damaged surface

XII → XIIa

XI → IX

IX → VIII

VIII → VII

VII → VIIa

VIIa → TFPI

Trauma

Tissue factor (extrinsic) pathway

Antithrombin

Prothrombin (II)

V

Protein C

Thrombomodulin

Active Protein C

Fibrinogen (I)

Fibrin (Ia)

Cross-linked fibrin clot

XIIIa → XIII

Common pathway
Antiphospholipid Syndrome

• Testing only when otherwise cryptogenic ischemic stroke, other suggestive features
• Defined by 1 clinical and 1 lab criteria met
  – Clinical
    • One or more clinical episodes of arterial, venous, or small vessel thrombosis
    • Pregnancy related: >1 unexplained deaths after 10 wks OR >1 premature births <34 wks from eclampsia or placental insufficiency OR ≥3 unexplained spont abortions < 10wks
  – Lab, persistently ↑ antibodies on repeated testing separated by at least 12 weeks
    • Lupus anticoagulant
    • Anticardiolipin antibody
    • Anti-β₂ glycoprotein antibody

Thromb Res. 2017 Mar;151 Suppl 1:S43-S47
**A Initial pathogenesis**

Antiphospholipid antibodies are produced by B cells

![Image showing B cell and antiphospholipid antibodies binding to a γ-GPI on an endothelial cell.](image)

**B Continued pathogenesis**

- Activation of inflammatory cells and endothelial cells
  - Neutrophil
  - Monocyte
  - NETosis

- Promotion of coagulation
  - Platelets
  - Clot

- Interference with trophoblasts and decidual cells
  - Trophoblast
  - Decidua

**C Examples of possible proinflammatory and prothrombotic changes induced by antiphospholipid antibodies**

- ↑ Complement activity
- ↑ E-selectin
- ↑ Tissue factor
- ↑ Vascular endothelial growth factor
- NETosis
- ↑ Expression of glycoprotein IIb/IIIa
- ↓ Tissue factor pathway inhibitor activity
- ↓ Protein C activity
- ↓ Fibrinolysis
- ↑ Complement activity
- ↓ Proliferation and syncitia formation
- ↓ Human chorionic gonadotropin
- ↑ Trophoblast apoptosis

**D Through multiple mechanisms, antiphospholipid-antibody activity results in:**

- Inflammation
- Vasculopathy
- Thrombosis
- Pregnancy complications
APS and Stroke, Treatment

- If meet criteria, assess risk level

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk†</td>
<td>A high-risk profile is defined as a positive LA test with or without a moderate-to-high titer of aCL or anti-β2GPI IgG or IgM.</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>A moderate-risk profile is defined as a negative LA test with a moderate-to-high titer of aCL or anti-β2GPI IgG or IgM.</td>
</tr>
<tr>
<td>Low risk</td>
<td>A low-risk profile is defined as a negative LA test with a low titer of aCL or anti-β2GPI IgG or IgM.</td>
</tr>
</tbody>
</table>

- Rx usually with warfarin (not DOACs) for secondary prevention

- Adding aspirin, higher INR, immunosuppression options if fail warfarin

NEJM 2018;378:2010-21
There were 11 (19%) events in the rivaroxaban group, and 2 (3%) events in the warfarin group.

Thromboembolic events occurred in 7 (12%) patients randomized to rivaroxaban (4 ischemic stroke and 3 myocardial infarction), whereas no event in those randomized to warfarin.

Major bleeding occurred in 6 patients: 4 (7%) in the rivaroxaban group and 2 (3%) in the warfarin group.
Central Nervous System Vasculitis

- Primary (PACNS, $1^\circ$) vs. secondary ($2^\circ$)
- Rare (esp. primary) cause of either ischemic or hemorrhagic stroke (sometimes both)
- Think of when...

- Cerebral ischemic episodes in different vascular beds, usually separated by time, with the presence of inflammatory changes in the cerebrospinal fluid (CSF)
- Cerebral ischemia in young patient with lack of traditional cerebrovascular risk factors for strokes
- Chronic meningitis without a demonstrated infectious or malignant etiology
- Subacute or chronic headache associated with cognitive dysfunction, usually with a history of aseptic meningitis
- Combination of unexplained focal and diffuse neurologic dysfunction

Vasculitis - Workup

- Routine stroke work up
- ESR, CRP, ANA, ANCA
  - nl in 1⁰, screen for 2⁰
- Lumbar puncture
  - Rarely normal in 1⁰, elevated cells or protein
  - Assists with DDx of infection
- Catheter angiogram
- Brain biopsy
Genetic Testing for Stroke
Lancet Neurol 2007; 6: 149–61
<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Gene</th>
<th>Stroke mechanism</th>
<th>Associated clinical features</th>
<th>Diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischaemic stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CADASIL</td>
<td>NOTCH3</td>
<td>Small-vessel disease</td>
<td>Migraine with aura</td>
<td>Mutational screening, skin biopsy</td>
</tr>
<tr>
<td>CARASIL</td>
<td>HTRA1</td>
<td>Small-vessel disease</td>
<td>Premature baldness; severe low back pain; spondylosis deformans or disk herniation</td>
<td>Mutational analysis</td>
</tr>
<tr>
<td>Fabry’s disease</td>
<td>GAL</td>
<td>Large-artery disease and small-vessel disease</td>
<td>Angiokeratoma; neuropathic pain; acroparaesthesia; hypohydrosis; corneal opacities; cataract; renal and cardiac failure</td>
<td>α galactosidase activity, mutational screening</td>
</tr>
<tr>
<td>MELAS</td>
<td>mtDNA</td>
<td>Complex (microvascular and neuronal factors)</td>
<td>Developmental delay; sensorineural hearing loss; short stature; seizures; episodic vomiting; diabetes; migraine-like headache; cognitive decline</td>
<td>Muscle biopsy, mutational analysis of mtDNA</td>
</tr>
<tr>
<td>Sickle-cell disease</td>
<td>HBB</td>
<td>Large-artery disease, small-vessel disease, haemodynamic insufficiency</td>
<td>Pain crises; bacterial infection; vaso-occlusive crises; pulmonary and abdominal crises; anaemia; myelopathy; seizure</td>
<td>Peripheral blood smear, electrophoresis, mutational analysis</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>CBS and others</td>
<td>Large-artery disease, cardioembolism, small-vessel disease, arterial dissection</td>
<td>Mental retardation; atraumatic dislocation of lenses; skeletal abnormalities (Marfan-like); premature atherosclerosis; thromboembolic events</td>
<td>Urine analysis, measurement of concentrations of homocysteine and methionine in plasma (mutational screening)</td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
<td>FBN1</td>
<td>Cardioembolism and arterial dissection</td>
<td>Pectus carinatum or excavatum; upper-to-lower segment ratio &lt;0.86, or arm-span-to-height ratio &gt;1.5; scoliosis &gt;20%; ectopia lentis; dilatation or dissection of the ascending aorta; lumbosacral dural ectasia</td>
<td>Clinical diagnosis (mutational screening)</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome type IV</td>
<td>COL3A1</td>
<td>Arterial dissection</td>
<td>Easy bruising; thin skin with visible veins; characteristic facial features; rupture of arteries, uterus, or intestines</td>
<td>Biochemical studies, mutational screening</td>
</tr>
<tr>
<td>Pseudoxanthoma elasticum</td>
<td>ABCC6</td>
<td>Large-artery disease and small-vessel disease</td>
<td>Skin changes (increased elasticity and yellow-orange papular lesions); ocular changes (angioid streaks); hypertension</td>
<td>Skin biopsy, mutational screening</td>
</tr>
<tr>
<td><strong>Intracerebral haemorrhage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial cerebral amyloid angiopathy</td>
<td>APP</td>
<td>Rupture of cortical cerebral small vessels</td>
<td>Cerebral lobar macrohaemorrhages and microhaemorrhages; white-matter lesions; cognitive impairment</td>
<td>Brain biopsy, mutational screening</td>
</tr>
<tr>
<td>COL4A1-related intracerebral haemorrhage</td>
<td>COL4A1</td>
<td>Rupture of cortical and subcortical cerebral small vessels</td>
<td>Infantile hemiparesis; congenital porencephaly; white-matter lesions; cerebral macrohaemorrhages and microhaemorrhages (lobar and non-lobar); transient ischaemic attacks</td>
<td>Clinical diagnosis, mutational screening</td>
</tr>
</tbody>
</table>

CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CARASIL=cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. MELAS=mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke. mtDNA=mitochondrial DNA.

Table 2: Mendelian (single-gene) disorders that include stroke in their phenotypic manifestations
Which/When Genetic Tests?

• Mendelian (single gene) causes of stroke recognized by
  – Familial aggregation
  – Relatively young age of onset
  – More severe clinical course
  – Higher recurrence rates

• Dx important in may allow for tailored management (sickle cell dz), and family counseling
Pharmacogenomics and Stroke

• Aspirin
  – COX-1 variants may effect platelet inhibition?

• Warfarin
  – VKORC1, CYP2C9, CYP4F2 variants effect warfarin metabolism
  – Suggested initial dosing based on genetic profile, but no good evidence effects outcomes – trials ongoing

• Identification may allow for personalization of medical regimen

Stroke. 2018 Oct;49(10):2541-2548
Pharmacogenomics and Stroke

• Clopidogrel
  – Loss of function CYP2C19*2,3,8 variants
    • Less clopidogrel metabolized to active form
    • Decreased platelet inhibition, more vascular events
    • DAPT may not be beneficial in carriers
    • FDA mandated **BLACK BOX WARNING**
  – Most data for MI, no good data for effecting therapy in stroke
  – No high level evidence supports routine testing
  – Could consider testing after recurrent stroke on clopidogrel, with options for higher dose or alternative agent

Stroke. 2018 Oct;49(10):2541-2548
Meta-analysis of Stroke risk x CYP2C19

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>*2, *3 or *8 Events</th>
<th>*3 or *8 Total</th>
<th>*1 or *17 Events</th>
<th>*1 or *17 Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M-H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHANCE 2016 (12)</td>
<td>80</td>
<td>854</td>
<td>41</td>
<td>609</td>
<td>36.1%</td>
<td>1.39</td>
<td>[0.97, 2.00]</td>
</tr>
<tr>
<td>Fang 2015 (25)</td>
<td>19</td>
<td>75</td>
<td>4</td>
<td>39</td>
<td>4.0%</td>
<td>2.47</td>
<td>[0.90, 6.76]</td>
</tr>
<tr>
<td>Han 2015 (14)</td>
<td>24</td>
<td>150</td>
<td>9</td>
<td>97</td>
<td>8.2%</td>
<td>1.72</td>
<td>[0.84, 3.55]</td>
</tr>
<tr>
<td>Hoh 2016 (16)</td>
<td>1</td>
<td>51</td>
<td>5</td>
<td>137</td>
<td>2.0%</td>
<td>0.54</td>
<td>[0.06, 4.49]</td>
</tr>
<tr>
<td>Jeong 2015 (24)</td>
<td>29</td>
<td>49</td>
<td>7</td>
<td>27</td>
<td>6.8%</td>
<td>2.28</td>
<td>[1.16, 4.50]</td>
</tr>
<tr>
<td>Jia 2013 (9)</td>
<td>5</td>
<td>160</td>
<td>1</td>
<td>99</td>
<td>0.9%</td>
<td>3.09</td>
<td>[0.37, 26.09]</td>
</tr>
<tr>
<td>Li 2016 (17)</td>
<td>5</td>
<td>150</td>
<td>8</td>
<td>118</td>
<td>6.7%</td>
<td>0.49</td>
<td>[0.17, 1.46]</td>
</tr>
<tr>
<td>Lin 2014 (8)</td>
<td>6</td>
<td>44</td>
<td>1</td>
<td>46</td>
<td>0.7%</td>
<td>6.27</td>
<td>[0.79, 50.02]</td>
</tr>
<tr>
<td>Qiu 2015 (10)</td>
<td>9</td>
<td>125</td>
<td>1</td>
<td>73</td>
<td>1.0%</td>
<td>5.26</td>
<td>[0.68, 40.65]</td>
</tr>
<tr>
<td>Spokony 2014 (22)</td>
<td>6</td>
<td>15</td>
<td>3</td>
<td>27</td>
<td>1.6%</td>
<td>3.60</td>
<td>[1.05, 12.36]</td>
</tr>
<tr>
<td>SPS3 2015 (11)</td>
<td>9</td>
<td>107</td>
<td>17</td>
<td>386</td>
<td>5.6%</td>
<td>1.91</td>
<td>[0.88, 4.16]</td>
</tr>
<tr>
<td>Sun 2015 (23)</td>
<td>51</td>
<td>377</td>
<td>14</td>
<td>248</td>
<td>12.7%</td>
<td>2.40</td>
<td>[1.36, 4.23]</td>
</tr>
<tr>
<td>Yi 2016 (18,21)</td>
<td>26</td>
<td>215</td>
<td>5</td>
<td>148</td>
<td>4.5%</td>
<td>3.58</td>
<td>[1.41, 9.11]</td>
</tr>
<tr>
<td>Zhang 2014 (15)</td>
<td>12</td>
<td>53</td>
<td>3</td>
<td>42</td>
<td>2.5%</td>
<td>3.17</td>
<td>[0.96, 10.51]</td>
</tr>
<tr>
<td>Zhu 2016 (19)</td>
<td>26</td>
<td>152</td>
<td>7</td>
<td>89</td>
<td>6.7%</td>
<td>2.17</td>
<td>[0.98, 4.80]</td>
</tr>
</tbody>
</table>

Total (95% CI): 2577/2185 (100.0%) 1.92 [1.57, 2.35]

Total events: 308/126

Heterogeneity: $\chi^2 = 17.42, df = 14$ (P = 0.23); $I^2 = 20$

Test for overall effect: Z = 6.27 (P < 0.00001)
CHANCE x CYP2C19

- RCT, 5170 pts, China
- High risk TIA or minor stroke, 24 hr window
- DAPT x 21 days vs. monotherapy
- 2933 patients had genetic testing

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Carriers(^a)</th>
<th>Noncarriers(^b)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>P Value</td>
</tr>
<tr>
<td>Stroke</td>
<td>Total (n = 1726)</td>
<td>Aspirin (n = 872)</td>
<td>Clopidogrel-Aspirin (n = 854)</td>
</tr>
<tr>
<td></td>
<td>174 (10.1)</td>
<td>94 (10.8)</td>
<td>80 (9.4)</td>
</tr>
<tr>
<td></td>
<td>Total (n = 1207)</td>
<td>Aspirin (n = 598)</td>
<td>Clopidogrel-Aspirin (n = 609)</td>
</tr>
<tr>
<td></td>
<td>115 (9.5)</td>
<td>74 (12.4)</td>
<td>41 (6.7)</td>
</tr>
</tbody>
</table>

JAMA. 2016;316(1):70-78
WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]. Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed “CYP2C19 poor metabolizers”). Tests are available to identify patients who are CYP2C19 poor metabolizers [see Clinical Pharmacology (12.5)]. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.
Emerging labs – Platelet Inhibition

• HTPR = high on-treatment platelet reactivity
  – Variously defined – most cross-sectional case-control, measure at one time compared to “normal”
  – Suggests less than optimal platelet inhibition
  – Various assays do not agree well with one another
  – Some evidence that if present, increases risk of subsequent ischemic vascular events, but mostly in CAD
  – No good evidence in stroke

• Some stroke patients have genetic polymorphisms that can alter effectiveness of anti-platelet medications
  – Does not account for much of observed HTPR

Platelets, 2015; 26(5): 402–412
## Prevalence of HTPR

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>Prevalence (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. According to antiplatelet used</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>0.23 (0.20, 0.28)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0.27 (0.22, 0.32)</td>
</tr>
<tr>
<td>Both</td>
<td>0.07 (0.05, 0.10)</td>
</tr>
<tr>
<td>2. According to ASA dosage</td>
<td></td>
</tr>
<tr>
<td>≤100 mg</td>
<td>0.24 (0.19, 0.29)</td>
</tr>
<tr>
<td>&gt;100 mg</td>
<td>0.24 (0.17, 0.32)</td>
</tr>
<tr>
<td>3. According to the method used</td>
<td></td>
</tr>
<tr>
<td>LTA</td>
<td>0.21 (0.16, 0.27)</td>
</tr>
<tr>
<td>LTA-ADP</td>
<td>0.19 (0.12, 0.27)</td>
</tr>
<tr>
<td>Multiplate platelet analyzer</td>
<td>0.21 (0.06, 0.41)</td>
</tr>
<tr>
<td>PFA-100</td>
<td>0.40 (0.31, 0.49)</td>
</tr>
<tr>
<td>Verify Now System</td>
<td>0.21 (0.16, 0.26)</td>
</tr>
<tr>
<td>4. According to measurement time</td>
<td></td>
</tr>
<tr>
<td>≤1 week</td>
<td>0.28 (0.23, 0.32)</td>
</tr>
<tr>
<td>&gt;1 week</td>
<td>0.21 (0.16, 0.26)</td>
</tr>
</tbody>
</table>
Risk of TIA/Stroke if HTPR

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agayeva et al</td>
<td>0.72 (0.28, 1.83)</td>
<td>5.75</td>
</tr>
<tr>
<td>Bennet et al</td>
<td>2.67 (0.66, 10.73)</td>
<td>3.70</td>
</tr>
<tr>
<td>Berrouschot et al</td>
<td>1.14 (0.15, 8.69)</td>
<td>2.11</td>
</tr>
<tr>
<td>Boncoraglio et al</td>
<td>1.05 (0.38, 2.93)</td>
<td>5.27</td>
</tr>
<tr>
<td>Cha et al</td>
<td>21.00 (1.22, 360.30)</td>
<td>1.20</td>
</tr>
<tr>
<td>Englyst et al</td>
<td>0.79 (0.25, 2.47)</td>
<td>4.73</td>
</tr>
<tr>
<td>Gengo et al</td>
<td>9.69 (4.40, 21.32)</td>
<td>6.67</td>
</tr>
<tr>
<td>Halawani et al</td>
<td>1.49 (0.63, 3.54)</td>
<td>6.21</td>
</tr>
<tr>
<td>Jeon et al</td>
<td>1.44 (0.71, 2.91)</td>
<td>7.24</td>
</tr>
<tr>
<td>Kim et al</td>
<td>1.28 (0.60, 2.06)</td>
<td>8.81</td>
</tr>
<tr>
<td>Lai et al</td>
<td>2.00 (0.54, 7.40)</td>
<td>4.00</td>
</tr>
<tr>
<td>Ozben et al</td>
<td>0.88 (0.42, 1.85)</td>
<td>6.98</td>
</tr>
<tr>
<td>Schwammenthaly et al</td>
<td>1.80 (0.43, 7.58)</td>
<td>3.53</td>
</tr>
<tr>
<td>Yu et al</td>
<td>3.09 (2.09, 4.58)</td>
<td>9.35</td>
</tr>
<tr>
<td>Zheng et al</td>
<td>2.28 (1.26, 4.12)</td>
<td>8.00</td>
</tr>
<tr>
<td>Subtotal (I-squared = 66.2%, p = 0.000)</td>
<td>1.78 (1.21, 2.62)</td>
<td>83.55</td>
</tr>
<tr>
<td>with estimated predictive interval</td>
<td>. (0.48, 6.56)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meves et al</td>
<td>1.55 (0.43, 5.57)</td>
<td>4.12</td>
</tr>
<tr>
<td>Nordeen et al</td>
<td>1.41 (0.49, 4.04)</td>
<td>5.14</td>
</tr>
<tr>
<td>Yi et al</td>
<td>2.81 (1.38, 5.71)</td>
<td>7.20</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.492)</td>
<td>2.12 (1.24, 3.62)</td>
<td>16.45</td>
</tr>
<tr>
<td>with estimated predictive interval</td>
<td>. (0.07, 67.77)</td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 60.5%, p = 0.000)</td>
<td>1.81 (1.30, 2.52)</td>
<td>100.00</td>
</tr>
<tr>
<td>with estimated predictive interval</td>
<td>. (0.58, 5.69)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
Emerging Labs – NT-proBNP

N-Terminal Pro-B-Type Natriuretic Peptide Is a Major Predictor of the Development of Atrial Fibrillation
The Cardiovascular Health Study

Kristen K. Patton, MD; Patrick T. Ellinor, MD, PhD; Susan R. Heckbert, MD, PhD;
Robert H. Christenson, PhD; Christopher DeFilippi, MD;
John S. Gottdiener, MD; Richard A. Kronmal, PhD
BNP – Brain Natriuretic Peptide

- First discovered in brain, largely produced in heart, both ventricular and atrial myocardium

- Increases natriuresis, diuresis and vasodilatation, thus resulting in a decreased cardiac workload

- NT-proBNP has a longer plasma half-life, exists at considerably higher concentrations, more stable at room temperature and current laboratory assays are highly sensitive and specific

- Widely used marker of CHF, but also elevated in atrial fibrillation

Circulation. 2009;120:1768-1774
Int J Cardiol. 2016 Oct 15;221:1031-8
• Blood available from 1029 APASS from WARSS
• NT-proBNP cutoff 750 used, 95\textsuperscript{th} percentile
  – Distribution highly skewed to right
  – Decision made prior to outcomes analyses
• 13 days median time from stroke to blood draw
• APASS patients verified as representative of WARSS
• NT-proBNP mean= 220 pg/mL, median 75 pg/mL
Amino Terminal Pro-B-Type Natriuretic Peptide, Secondary Stroke Prevention, and Choice of Antithrombotic Therapy

W.T. Longstreth Jr, MD, MPH; Richard A. Kronmal, PhD; John L.P. Thompson, PhD; Robert H. Christenson, PhD; Steven R. Levine, MD; Rebecca Gross, BS; Robin L. Brey, MD; Richard Buchsbaum; Mitchell S.V. Elkind, MD, MS; David L. Tirschwell, MD, MSc; Stephen L. Seliger, MD, MS; J.P. Mohr, MD, MS; Christopher R. deFilippi, MD

NT-proBNP ≤ 750 pg/mL

NT-proBNP > 750 pg/mL
ATRIAL CARDIOPATHY

VASCULAR RISK FACTORS

NON-ATRIAL STROKE MECHANISMS

STROKE

ATRIAL FIBRILLATION

Atrial Cardiopathy $<\rightarrow>$ Stroke

Markers of atrial cardiopathy $<\rightarrow>$ stroke, independent of AF
- P-wave terminal force in ECG lead $V_1$ (PTFV$_1$)
- NT-proBNP
- Left atrial size/function on echocardiogram

ARCADIA: Only ESUS + Atrial Cardiopathy

- AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke
- Primary Hypothesis: apixaban is superior to aspirin for prevention of recurrent stroke in patients with ESUS and atrial cardiopathy
- Secondary hypothesis: benefit of apixaban increases with severity of atrial cardiopathy
  - Personalized prediction of risk/benefit
  - May help set stage for primary prevention trial
Summary

• Emergency labs
  – Do NOT need to wait for creatinine or coags to come back before giving tPA, unless some suspicion of abnormality (e.g. hx Afib)
  – Coags can rapidly assess effects of all anticoagulants
  – Can lead to use of reversal agents in ICH
  – Platelets not useful in ICH on antiplatelet med

• Admit labs – risk stratification
  – Blood sugar goal <180, less aggressive, OK

• Hypercoagulable state testing
  – Overall much less commonly done
  – Young patients especially without clear cause, or older patients with unusual recurrences
  – APS: if found treat with warfarin, not DOAC

• Vasculitis: rarely done, blood work, LP, angio and possibly even brain biopsy

• Genetic testing: rarely done, strong family hx, possible pharmacogenomics applications

• Emerging labs
  – Platelet function assays: possibly useful if recurrent events despite good therapy, but many research gaps remain
  – NT-proBNP: emerging biomarker, being tested in clinical trial
Thank you for your attention...