Use of NOACs for Treatment of Cerebrovascular Disease (but not Afib)

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All of this is way, way, off label.....but .....

Conditions to Consider

1. Cerebrovascular dissection (with or without a stroke)
2. Cerebral venous thrombosis
3. Hypercoagulable states causing ischemic stroke
4. High grade intracranial stenosis

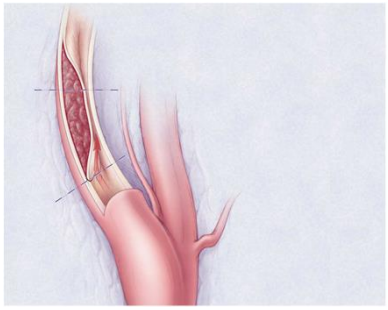
Dissections Causing Stroke

- Presenting Sx often neck or head pain
- Often complain of very severe pain
- History of neck trauma present in 50% of cases
  - MVA, chiropractic neck manipulation, deep massage, hair care, sneezing, pregnancy
- Some patients may have underlying condition such as FMD, connective tissue disorder
- Typically occurs in young patients

Mechanisms of stroke in dissection

- Most common process is artery to artery emboli—seen in at least 60-70% of cases
- Vessel occlusion is other mechanism
- Layers of dissection
  - Between intima and media
  - Between media and adventitia—may produce pseudo aneurysms
- Major risk of stroke appears to be at the time of the dissection or soon thereafter

Anatomy of Dissection



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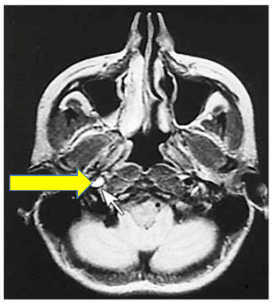
MRI of Dissection

Subacute blood in wall of vessel appears white

Mural thrombus



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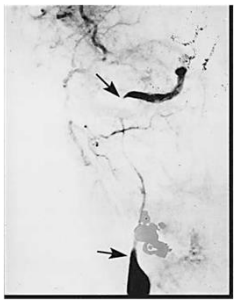
Angiogram of Dissection



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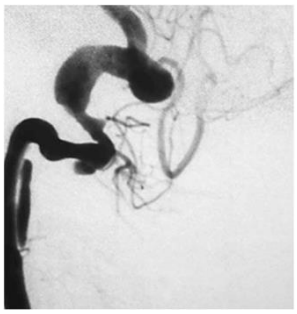
Complex Dissection



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Treatment of Dissection

- Typically use IV heparin(few days) followed by oral warfarin for 3-6 months
  - If intracranial vessels involved, do LP first to r/o SAH
- If the dissection is very small and there is no stroke, aspirin would also be appropriate
- Repeat MRA or CTA in 3 months
  - If healed change to ASA
  - If still present, do another 3 months of warfarin
- d/c warfarin after 6 months unless large pseudoaneurysm with clots
  - Healing largely complete

Potential Advantages of Using NOACs

- Avoid prolonged hospitalization
- Avoid using IV heparin and bridging to warfarin therapy
- NOACs are easier to use than warfarin
  - No need for dose titration
  - No need for routine blood monitoring
  - No common food or drug interactions
  - Lower rate of CNS bleeding c/w warfarin
- Might be better tolerated in a younger population

Cerebral Venous Thrombosis

- Typically occurs in large cerebral veins
  - Superior sagittal sinus
  - Transverse, sigmoid, jugular veins
  - Can affect deep venous system also
  - Rarely affects cortical veins
- Associated with hypercoagulable states in most cases
  - Coagulation disorders, pregnancy, dehydration, IBD
  - May have occult malignancy

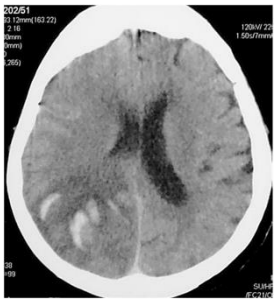
Causes and Work Up of Patients with CVT

- Hypercoagulable state
  - Check coags, LA, ACA, full panel
  - Check d-dimer
- Often ppt by OCPs or HRT
- Can be caused by dehydration, head trauma, IBD
- CVT = DVT; always check LEDs in patients with CVT

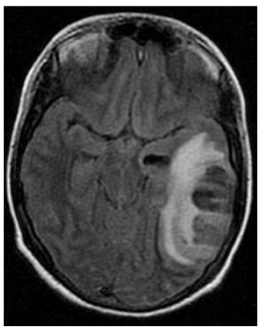
Strokes caused by CVT

- Venous infarction
  - Edema/mass effect, not in a typical arterial territory, some bleeding, seizures
  - Often mistaken for tumor, infection
- Can produce typical infarction
- Can also cause hemorrhagic transformation, ICH or SAH
- Evidence of increased intracranial pressure
  - Headache, Sz, nausea/vomiting
- If severe can cause herniation and death

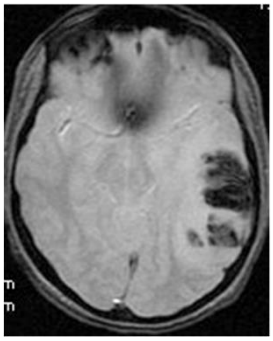
Brain CT--CVT



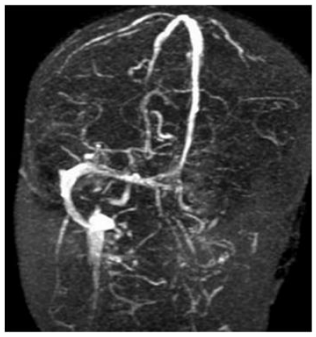
MRI of CVT



MRI—GRE image showing hemorrhage



MRV showing Venous Occlusions



CVT—Treatment Options

- IV heparin or LMW heparin, followed by warfarin
- Treat underlying condition
- Treat bleeding or ICP if present

- Potential advantages of NOAC therapy
  - All of the advantages of NOT using warfarin
  - Potentially less CNS bleeding
  - Shorter hospitalization (if patient otherwise stable)
  - Reduced chances for medication errors

Supporting Data for NOACs in CVT

- Essentially all are FDA approved for treatment and/or prevention of DVT
- DVT and CVT share several features
  - Often caused by ppt factors, hypercoag state
  - Can involve small, medium, or large veins
  - Risk of recurrence if not anticoagulated
  - May need prolonged therapy in some cases
  - I have personally used NOACs in several patients with CVT, especially with HT
    - Very safe
    - No bleeding complications
    - Often used low dose regimen

Coagulopathies Causing Strokes

- Antiphospholipid antibodies
  - LA
  - ACA
- Protein C, S deficiency
- AT III deficiency, Factor V Leiden
- Hormone therapy (oral contraceptives, HRT)
- Cancer
- Inflammatory bowel disease

Coagulopathies and Stroke

- Many occur spontaneously
- May be a + family history or prior clotting events
- In general, venous clots are more common than arterial clots
- Can be associated with other conditions:
  - Lupus
  - Autoimmune disorders
  - Inflammatory bowel disease

Use of NOACs for Coagulopathies

- Limited data (case reports)
- Need to identify coagulopathy and agent
  - Direct thrombin inhibitor – Dabigatran
  - Factor Xa inhibitor – most others
- Duration of therapy and optimal dosing unknown in many cases
- Is being studied for some conditions

NOACs for Intracranial Stenosis

- High-risk population
- Reucrrent stroke in 22% of patients after 2 years
- Stenting failed to reduce event rates (SAMMPRIS Study)
- Medical therapy alone seems best
- Still high risk of recurrent events

Original Article

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The NEW ENGLAND JOURNAL of MEDICINE

New Data from COMPASS Study may provide some insights

- Enrolled patients with stable atherothrombotic disease
- > 27,000 patients
- 3 treatment groups:
  - Low dose Rivaroxaban 2.5 mg BID + ASA
  - Rivaroxaban 5 mg BID alone
  - ASA alone
- Primary outcome was Stroke, MI, VD

COMPASS Results

Table 2. Efficacy Outcomes.*

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)
	number (percent)		
Primary outcome: CV death, stroke, or myocardial infarction†	379 (4.1)	448 (4.9)	496 (5.4)
Secondary outcomes‡			
Ischemic stroke, myocardial infarction, ALI, or death from CHD	329 (3.6)	397 (4.4)	450 (4.9)
Ischemic stroke, myocardial infarction, ALI, or CV death	389 (4.3)	453 (5.0)	516 (5.7)
Death from any cause	313 (3.4)	366 (4.0)	378 (4.1)
Other outcomes§			
CV death	160 (1.7)	195 (2.1)	203 (2.2)
Non-CV death	153 (1.7)	171 (1.9)	175 (1.9)
Death from CHD	86 (0.9)	128 (1.4)	117 (1.3)
Stroke¶	83 (0.9)	117 (1.3)	142 (1.6)
Ischemic or uncertain type	68 (0.7)	91 (1.0)	132 (1.4)
Hemorrhagic	15 (0.2)	27 (0.3)	10 (0.1)

Implications

- Low dose NOAC therapy combined with low dose ASA appears effective and relatively safe for long term therapy
- Might this approach be useful for patients with symptomatic intracranial atherothrombotic disease?
- Could be more effective than dual antiplatelet therapy
- Me and others have suggested trials that focus on this high risk population to the NOAC manufacturers