Sickle Cell Disease and Venous Thrombosis

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Disclosure

• No financial conflicts of interest

• However, my academic clinical workload:
  – 80-90% of patients seen in consultation for VTE or other types of thrombosis, 200-250 new cases/yr
  – The other 10-20% have hemoglobinopathies, some of whom have had VTE
Venous Hemostasis

Coagulation factor-dependent

- Initiated by activation of coagulation on altered vessel surface
- Augmented by stasis, permits factor/surface interaction
- Limited by endogenous anticoagulants
As for other complex chronic medical conditions, multiple risk factors for VTE present in patients with sickle cell disease.
The Many Processes in SCD

Reperfusion Injury Physiology

Inflammation

macrophage & immune activation

oxidant generation

NO depletion

coagulation activation

endothelial activation

RBC sickling

vascular stasis

hemolysis

Hebbel, Cardiovasc Hematol Disord Drug Targets 9:271, 2009
Coagulation Activation ≠ VTE

• Various changes/markers noted
  – ↑ ultralarge vonWillebrand factor (vWF) multimers
  – ↑ plasminogen activator inhibitor-1 (PAI-1)
  – ↑ thrombin-antithrombin complexes (TAT), prothrombin fragment F1.2, D-dimer

• No hypercoagulability noted on global fctn tests
  – Conflicting data thrombin generation

• No correlation with clinical events
  – VTE or pulmonary hypertension

Lim, Curr Opin Hem 20:472, 2013; Ataga, Haematologica 84:1481, 2009
VTE is not “Vaso-Occlusion”

- Extent of macro-vascular venous stasis in SCD has not been well-described
  - Small vessel vaso-occlusion mediated by cellular adhesion and endothelial activation
  - Most often thought to be micro-circulation or post-capillary venule
    Cell/cell adhesion and abnormal adhesion of both red cells and leukocytes to endothelium
    (sickle cell mouse)

- No evidence VTE is “sickling in the veins”
Contributors to Stasis in SCD

- Indwelling vascular appliances
- Surgery
  - Anesthesia
  - Immobility
  - Higher-risk surgeries
    - Major abdominal surgery
    - Orthopedic surgery
- Immobility during hospitalization for severe medical illness
- Local compression in late stages of pregnancy

*Clin Case Rep* 3:170, 2015
Mechanisms for Endothelial Injury

• Activation, injury of endothelium by
  – Heme: induces TF
  – Reduction in NO: less inhibition of TF, adhesion molecules
  – Inflammation/cytokines
  – Ischemia-reperfusion injury: oxidative processes
  – Cell adhesion: activates endothelium

• But studies are of microvasculature, not veins

• Circulating microparticles (of RBCs in particular) may be a key surface

Inherited Thrombophilia in SCD

- Known conditions characterized from northern European populations
  - Factor V Leiden, prothrombin G20210A, protein C/S/AT def
- Low frequency and no association with thrombosis in African, West Indies, Jamaican, Maghrib, Brazilian, east Saudi Arabian SCD populations
  - Increased prevalence of FVL and/or PGM in southern Iranian, Indian and Lebanese patients with SCD but association with clinical VTE not reported

Low Levels of Natural Anticoagulants

• Inconsistent reports of low values (40-50% activity)
  – Values often higher than those seen with inherited deficiencies
• No association with VTE reported
• As seen in any human, may occur related to
  – Consumption with chronic activation of the clotting cascade
  – Inflammation (↓ free PS)
  – Concomitant liver disease
  – Consumption during acute thrombosis
  – OCP use/pregnancy
  – Anticoagulant exposure

Acquired Thrombophilia

• Antiphospholipid antibodies: speculated to arise in response to RBC membrane PL disruption
  – One study showed low titer IgG antibodies to cardiolipin and phosphatidylserine
  – No association with VTE

• Hyperhomocysteinemia (?) – weak venous risk factor
  – Mean Hcy higher in SCD, but modestly (mean 9.7 vs 8.5 in once study), normal in 80%
  – tMTHFR polymorphisms irrelevant unless associated with high homocysteine

Other Acquired Hypercoagulability

- Estrogen exposure
  - Contraception/HRT
  - Pregnancy
- Surgery/Anesthesia
Interval Summary: Risk For VTE in SCD

- Venous stasis, but not due to “sickling”
  - No evidence of unique factors in SCD
  - But exposed to interventions (e.g. catheters, surgery)

- Endothelial activation/injury, but maybe microparticles are key

- Hypercoagulability
  - No association with known genetic thrombophilia
  - Acquired changes may shift balance in a way that predisposes the coagulation system toward VTE
Overall Risk of VTE in SCD

• Lifetime Risk Estimates from Atherosclerotic Risk in Communities (ARIC): ≥45 year-olds
  – African Americans: 11.5%
    • Sickle cell trait or disease: 18.2% (3.8-25.1)
    • No HbS: 11.0% (8.3-12.5)
  – Homozygous or heterozygous FVL: 17.1% PGM: 6.3%
  – Obesity: 10.9%
  – Blood type non-O: 8.9%


• About as bad as FVL, not distinguishing provoked vs. unprovoked, trait vs. disease
Risk of VTE in SCD

• Cumulative risk estimates: 11-18% by age 30-40
• Risk of pulmonary embolism (PE)
  – Overall: 0.22-0.25%, uncorrected for race
  – Hospitalized patients: 0.44% (vs. 0.12% of African American)
• Annualized risk ≤1%/year or 100 person-years:
  – 0.52 – 1%/year combining all genotypes
  – 0.76/year for HbSS/β0thal
• When documented, most are provoked events


Risk For VTE in SCD

- California administrative dataset analysis
  - 1991-2013: 6237 SCD patients, median f/u 15 years
  - Compared to African-American asthma patients
  - Both classified as:
    - Severe: At hospital $\geq$ 3 times/year, n = 2654
    - Less Severe: Admitted less, n = 3583
  - <65 years of age

- Overall VTE incidence in cohort: 11.2%
  - 23% upper extremity DVT
  - 52% pulmonary embolism (PE)
  - Risk higher in women (12.6%) than men (9.5%)

Brunson, Br J Haem 178:319, 2017
Risk For VTE in SCD: California Cohort

- Higher rates than the asthma cohort

By age 40:

Severe SCD: 17.1%
Less severe SCD: 6.8%, which = severe asthma

Brunson, Br J Haem 178:319, 2017
Risk For VTE in SCD: California Cohort

• Potential provoking factors
  – 50% occurred with 60 days of hospitalization
    • average length of stay ≥3 days
  – 4.3% of VTE in women associated with pregnancy code
  – 41% of upper extremity VTE associated with prior central line placement

• Not reported in this study:
  – Complications during hospital stay (e.g. pneumonia)
  – Estrogen use
  – Co-morbidities (e.g. SLE)

Brunson, Br J Haem 178:319, 2017
Risk For VTE in SCD: California Cohort

- Recurrent VTE in SCD: 31% at 5 years (anticoagulation use not noted)

Brunson, Br J Haem 178:319, 2017
VTE in SCD: California Cohort

• Increased risk of all-cause mortality if:
  – More severe disease: HR 1.83 (1.61-2.09)
  – Had incident VTE: HR 2.88 (2.35-3.52)

• Risk of death **not** higher for those with **recurrent** VTE

• **Not** increased death due to thrombosis or hemorrhage

What to Do About VTE in SCD?

• Prevention
  – Everyday life
  – High risk settings

• Treatment
  – Anticoagulant choices
  – Acute treatment
  – Duration
Long-Term Anticoagulation Even Without History of VTE? Probably Not

- Not done for known hypercoagulable states:
  - Cancer, even when rates approach 30%
  - Other severe medical illnesses, e.g. systemic lupus erythematosus (SLE), even when antiphospholipid antibodies are present

- Not considered for known thrombophilias

- Best guess at a risk for unprovoked VTE: <1%/year
  - Equal to or less than oft-quoted risk of complications related to chronic anticoagulation (1%/year)
Higher-Risk Circumstances: Catheters

• Important subset of VTE in SCD:
  – Retrospective single institution: 25% of all VTE
  – California dataset: 9% of all VTE

• 0.49 – 0.99 per 1,000 catheter days (kids/adults)
  – Said to be most common risk factor in kids

• Temporary catheters for apheresis (adults)
  – 1% VTE if internal jugular, 9% if femoral

Systemic Prophylactic Anticoagulation for Indwelling Catheters? Probably Not

• Not done for other groups at risk
  – Risk of CVC-thrombosis in cancer patients: 1-6%
  – Risk with PICC lines 0.2 per 1000 catheter days

• Low-dose warfarin and LMWH not better than placebo to reduce risk

• Recommend treatment once a thrombosis occurs, generally acceptable to leave the line in place if it works

Higher Risk Circumstances: Hospitalization – Prophylaxis? Yes

• Hospitalization/Acute Medical Illness
  – Study demonstrated 4x increased risk of PE (0.44 vs 0.12) for SCD discharges as compared to gen’l AA population
  – California study suggests association with hospitalization (50% within 60 days)

• SCD likely similar to other acute severe illnesses: meets usual criteria for routine prophylaxis when inpatient

Inpatient VTE Prophylaxis in SCD

- Single US institution retrospective cohort
  - 116 patients with SCD over 2 year period
    - 86% had prophylaxis ordered, usually enoxaparin 40 mg/day
    - 43% of scheduled doses not given due to patient refusal
  - 8 (6.9%) developed VTE
    - 3 upper extremity, 2 lower extremity
    - 2 pulmonary embolism
  - All had central venous catheters and all but one has history of multiple admissions
  - One episode of GI bleeding, no HIT

Kelley, J Thromb Thrombolysis 43:463, 2017
### Higher Risk Circumstances: OCPs

- Risk of VTE in women with SCD who use estrogen-based contraception has not carefully studied

<table>
<thead>
<tr>
<th>Study Authors, Publication Year (Country)</th>
<th>Estrogen Dose</th>
<th>Study Participants</th>
<th>Study Design</th>
<th>Thrombotic Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutcher et al 1981 (US)</td>
<td>&gt; 50 mcg estrogen</td>
<td>31 (70 pt-yrs)</td>
<td>Prospective cohort</td>
<td>None reported</td>
</tr>
<tr>
<td>Lutcher et al 1986 (US)</td>
<td>High and low-dose estrogen</td>
<td>71 (276 pt-yrs)</td>
<td>Prospective cohort</td>
<td>None reported</td>
</tr>
<tr>
<td>Howard et al 1993 (UK)</td>
<td>Not specified</td>
<td>67 (148 pt-yrs)</td>
<td>Retrospective cohort, survey</td>
<td>DVT (2)</td>
</tr>
<tr>
<td>deAbbood 1997 (Panama)</td>
<td>Low-dose estrogen</td>
<td>14</td>
<td>Randomized</td>
<td>None reported</td>
</tr>
</tbody>
</table>

So, Avoid Estrogen-Based OCPs in SCD Because of VTE Risk? Probably Not

• SCD: ~1.3/100 pts years (??, maybe per last slide)
• Thrombophilia families (other genes likely present)
  – FVL, PGM: 2 per 100 pt-yr
  – PC/PS/AT: 25 per 100 pt-yr
• Screening is not recommended for inherited thrombophilia prior to OCP use; personal & family history considered
• SCD may be weaker risk factor; WHO category 2 (benefits likely to outweigh the risks)

Higher Risk Circumstances: 
Pregnancy

- Multi-state Medicaid Study of SCD
- Thrombotic complications of pregnancies:

<table>
<thead>
<tr>
<th>Event</th>
<th>SCD</th>
<th>No SCD/+CC</th>
<th>No SCD/-CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>2%</td>
<td>0.8%</td>
<td>0.3%</td>
</tr>
<tr>
<td>PE</td>
<td>1.1%</td>
<td>0.5%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>0.8%</td>
<td>0.8%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

- No increased risk of stroke as compared to other diseases, but higher than controls
  - Absolute risk? 1 in 125 pregnancies

Boulet. *Matern Child Health J* 17:200; 2013
Higher Risk Circumstances: Pregnancy

• Analysis of 14,335 pregnancies complicated by PE/DVT in Healthcare Cost and Utilization Project (HCUP): 1.72 per 1000 deliveries in SCD

• Associated medical risk factors (Odds Ratio)
  – Thrombophilia  51.8
  – History of PE/DVT  24.8
  – Lupus  8.7
  – Sickle cell disease  6.7
  – Obesity  4.0
  – Diabetes  2.0

Higher Risk Circumstances: Pregnancy

- Prospective study of 60 Brazilian women: 6% DVT
- Hospital discharge data for pregnant women with SCD and VTE: 2.8%
  - 71.4% occurred post-partum
  - Higher if acute co-morbidity

So, Prophylaxis During Pregnancy for Women with SCD? Probably Not

- Risk in SCD may be 0.2-5% per pregnancy, lower than SLE, for which prophylaxis is not recommended in absence of APS
- May be comparable to women with FVL
  - Testing pregnant women for FVL not recommended
  - Prophylaxis not recommended unless there is a personal history of VTE
- However, if they are hospitalized and sick, prophylaxis as for any woman

Higher Risk Circumstances: Major Surgery – Prophylaxis? Yes

- No data in SCD
- Based on “gestalt”, could place those with SCD in category of increased risk of VTE, apply prophylaxis accordingly
  - Major abdominal surgery
  - Orthopedic surgery
Interval Summary: Higher Risk Circumstances

- If history of VTE, manage as for any population with history of VTE
- If no history of VTE, then manage as for others with mild “hypercoagulable” states (e.g. FVL) or systemic illnesses (e.g. SLE):
  - Would not anticoagulate for indwelling lines
  - Would not automatically avoid estrogen-based OCPs
  - Would not offer prophylaxis during pregnancy
  - Would use prophylaxis for
    - Acute hospitalizations
    - Major abdominal and orthopedic surgery
Treatment for VTE in SCD

- In general, as for non-SCD populations:
  - LMWH+VKA or DOACs

- Mind the renal dysfunction when using low molecular weight heparin (LMWH) and direct oral anticoagulant agents (DOACs)

## Renal Function and DOACs

- Renal elimination

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Dabigatran</th>
<th>Etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-Life</td>
<td>7-17 h</td>
<td>3.2-11 h</td>
<td>8-15 h</td>
<td>9-10 h</td>
<td></td>
</tr>
<tr>
<td>Elimination</td>
<td>80% renal</td>
<td>66% renal</td>
<td>28% renal</td>
<td>50% renal</td>
<td></td>
</tr>
</tbody>
</table>

- Impact of hyperfiltration in young SCD patients?
- Impact of (unrecognized) renal dysfunction?
# DOAC Dosing for VTE: Varies by Timing, Renal Function

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dabigatran Etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>150 mg bid</td>
<td>20 mg/dy</td>
<td>5 mg bid</td>
<td>60 mg/dy CrCl 50-95</td>
</tr>
<tr>
<td>↓ renal fctn (GFR)</td>
<td>CrCl 15-30: 75 mg bid</td>
<td>CrCl 15-30: 15 mg/dy</td>
<td>2.5 mg bid</td>
<td>30g mg/day CrCl 15-50</td>
</tr>
</tbody>
</table>

| Acute VTE*                  | LMWH x 5-10 days     | 15 mg bid x 21 dys | 10 mg bid x 7 dys | Parenteral x 5-10 dys |
| “Treatment” VTE*            | 150 mg bid           | 20 mg/day          | 5 mg bid          | 60 mg/day CrCl 15-50  |

| Reduce recurrence*          | 10 mg/day            | 2.5 mg bid        |          | 30 mg/dy CrCl 15-50 <60 kg |

*no comment in US labeling about dose reduction for renal insufficiency (!?)
Use of DOACs in Sickle Cell Disease

- Single case series of rivaroxaban

  - One “failure despite adherence” (recurrent VTE): switched to wararin
  - One CNS hemorrhage/infarction attributed to seizures: switched to apixaban

Ann Pharmacotherapy 51:357, 2017
Duration of Anticoagulation in SCD

• Management of a VTE episode: 3 months
  – No data to support longer discrete period of time, even for PE

    ACCP Guidelines, Chest 2016; 142:315

• Then for as long as a person wants to avoid the risk of recurrence
  – And is more concerned about recurrent clotting than risk of bleeding
Long-Term Anticoagulation in SCD: Continue (?)

• Recurrence after unprovoked events or “severe” SCD:
  – California study ($\geq 3$ hosp/year): 37% at 5 years
    
    (but many events may be been provoked)
  – In all studied populations: 25% risk at 2 years, 40-50%
    10 years without anticoagulation


• Recurrence if persistent risk factors: “high”
  – Central venous catheter still in place
  – Continued estrogen exposure
  – Chronic inflammatory co-morbidities
Long-Term Anticoagulation in SCD: Stop After 3 Months (?)

• Initial episode associated with transient risk factor
  – 5-20% risk of recurrence over 10 years without anticoagulation in other populations
  – Potential scenarios: VTE only in setting of
    • Pregnancy
    • Estrogen use, which has been discontinued
    • Major surgery
    • Particularly severe hospitalization

• Fastidious attention to prophylaxis in high-risk settings
Summary

• Sickle cell disease is a severe systemic illness characterized by inflammation, vascular injury and the need for medical interventions
• As such, anticipate an increased risk of VTE and remain vigilant
• However, data needed before considering routine preventative anticoagulation beyond what is based on personal history and risk factors as for other populations
• Use DOACs with careful consideration of renal function (hyper- and hypo-) until we can measure them
Questions?