Health Disparities in Venous Thromboembolism

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@MaryCushmanMD
Race Differences

In this talk, reference to race is in the context of understanding socio-cultural determinants of health of the studied population.

In some cases, I discuss genetic markers more common in those of African Ancestry, which in turn are more common in Black than White people in the United States.
Research to Practice

Epidemiology Studies

Human Testing
Trials / Pragmatic Trials
Quality / Implementation Science
Research to Practice Challenge

Epidemiology Studies

Action – what can YOU do?
Epidemiology to Practice

- We won’t have a trial for every situation
- Need to adapt knowledge to clinical situations
  - “How do we prevent VTE in different risk groups”
- Epidemiology research can help
Let’s get on the same page
3rd leading vascular diagnosis, affects up to 900,000 annually in US

Lifetime risk at age 45: 8%

60-100,000 deaths annually

Significant morbidity
- Treatment complications – Major bleeding: 6%
- Long term sequellae
  - Post-thrombotic syndrome: 30-40%
  - Chronic thromboembolic pulmonary hypertension: 1-8%
VTE Risk Factor Model

Intrinsic Thrombosis Risk

- Anticoagulant deficiencies
- Factor V Leiden
- Prothrombin 20210A
- Higher FVIII, XI
- Non-O Blood Group

Triggering Factors

- Pregnancy
- Surgery
- Immobilization, Trauma

Acquired RFs

- Age
- Prior VTE
- Cancer
- Obesity
- Venous insufficiency
- Hormones
- Elevated D-dimer
- Kidney Disease
- Others

Prophylaxis

Folsom A, Cushman M
Data on Racial Differences in VTE
Defining Racial Differences in VTE

Administrative data is a good starting place

## Defining Racial Differences in VTE

Administrative data is a good starting place

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Incidence per 100,000</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>230</td>
<td>reference</td>
</tr>
<tr>
<td>Black</td>
<td>293</td>
<td>1.27 (1.07-1.51)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>139</td>
<td>0.60 (0.54-0.67)</td>
</tr>
<tr>
<td>Asian / Pacific Islander</td>
<td>60</td>
<td>0.26 (0.22-0.30)</td>
</tr>
</tbody>
</table>

VTE Consequences May be Worse Among Black People

- Higher burden of PE than White people
- Higher case fatality than White people
- Higher readmission rate after PE

White R. Blood Coag Fibrinol 2005
Aujesky D. Arch Intern Med 2009
PE Rising as Cause of Death: CDC WONDER

2x higher risk in Black people

Rising in all groups since 2008

Martin K. JAHA 2020; e016784
Administrative Data

- Case and exposure misclassification
- Availability of other risk factor data limited
- Can’t always address questions of etiology: Why are there racial differences in VTE rate?
  - Health care attitudes?
  - Socioeconomic factors?
  - Risk factor / susceptibility differences?
  - Neighborhood / environment factors?
  - Structural racism
  - Race-specific risk factors?
Racial Differences in VTE

Observational Studies can help us understand
Cohort Study

Risk Factor Assessment
n = 22,000

VTE Outcomes
n = 900
The LITE Study

- 21,680 participants
- Age 45 - 100
- Baseline blood collection
- Long term follow up

Cushman M. Am J Med 2004
**Racial Disparity in VTE: LITE**

<table>
<thead>
<tr>
<th></th>
<th>Incidence per 1000 PY</th>
<th>HR (95% CI)</th>
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<tr>
<td>White</td>
<td>1.20</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Black</td>
<td>1.78</td>
<td>1.6 (1.2-2.2)</td>
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*HR slightly higher for provoked than unprovoked VTE*

*Is trauma community aware?*

Tsai A. Arch Intern Med 2002;162
## Racial Disparity in VTE: LITE

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<tr>
<td>White</td>
<td>1.20</td>
<td>1.0 (ref)</td>
<td>6.9 (5.9-7.7)</td>
</tr>
<tr>
<td>Black</td>
<td>1.78</td>
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<td>11.5 (8.8-13.1)</td>
</tr>
</tbody>
</table>

**HR slightly higher for provoked than unprovoked VTE**

**Is trauma community aware?**

Tsai A. Arch Intern Med 2002;162
Bell Am J Med 2016
VTE in Trauma??

No data I’m aware of on racial differences in incidence, use of, or effectiveness of prophylaxis.

Is race reported consistently in trials and observational studies?

Such data would be relevant to this week’s work.
Racial Differences in Thrombosis Risk

Little understanding of reasons

Compared to White people, Black people have:

- Lower prevalence of common thrombophilias
- Same likelihood of positive family history
- More adverse levels of hemostatic factors
  - D-dimer, factor VIII, protein C, prothrombin
  - Thrombin generation
  - Age related increase in D-dimer greater

Dowling, JTH 2003
Lutsey P, JTH 2006
Lutsey P, JTH 2009
Cushman unpublished
Numerous Hypotheses and Research Questions to Consider

- Differential susceptibility to risk factors
- Different prevalence of risk factors as mediators
- Race-specific risk factors
Differential Susceptibility to Risk Factors
Nested Case Control Study

Risk Factor Assessment, Blood samples → Control Group → Outcomes of Interest

Study only those with outcomes and a subset of the rest
# VTE Risk Factors by Race: LITE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>White (368+ cases)</th>
<th>Black (134+ cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer Q4</td>
<td>3.0 (2.1-4.3)</td>
<td>2.3 (1.1-4.7)</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>3.4 (2.2-5.5)</td>
<td>6.3 (0.6-60)</td>
</tr>
<tr>
<td>Non-O blood group</td>
<td>1.6 (1.2-2.1)</td>
<td>1.5 (1.0-2.3)</td>
</tr>
<tr>
<td>High Factor VIII</td>
<td>1.6 (1.1-2.4)</td>
<td>1.6 (1.1-2.4)</td>
</tr>
<tr>
<td>Low PTT</td>
<td>2.0 (1.0-4.1)</td>
<td>3.2 (1.2-8.8)</td>
</tr>
<tr>
<td>High Factor XI</td>
<td>1.3 (1.0-1.9)</td>
<td>1.5 (1.1-2.7)</td>
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</table>
Mediation Analysis of Racial Differences
Mediation of Racial Difference by Obesity Status

<table>
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<tr>
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<th>HR VTE by Study</th>
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<tr>
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<td>ARIC</td>
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<td>HR Black vs White</td>
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Zakai N. Circulation 2014
# Mediation of Racial Difference by Obesity Status

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<td>HR Black vs White</td>
<td>1.61 (1.33-1.95)</td>
<td>1.82 (1.25-2.65)</td>
</tr>
<tr>
<td>Add BMI to model</td>
<td>1.38 (1.13-1.68)</td>
<td>1.57 (1.07-2.31)</td>
</tr>
<tr>
<td></td>
<td>37% mediation</td>
<td>30% mediation</td>
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Zakai N. Circulation 2014
Mediation of Racial Difference by other Risk Factors: ARIC, 10-22y F/U

| HR Black vs White, age, sex adj | 2.04 (1.76-2.37) |

Mediation of Racial Difference by other Risk Factors: ARIC, 10-22y F/U

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<td>Weight</td>
<td>21% reduction</td>
</tr>
<tr>
<td>Income</td>
<td>26% reduction</td>
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<tr>
<td>Factor VIII</td>
<td>19% reduction</td>
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HR Black vs White, age, sex adj: 2.04 (1.76-2.37)

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</tr>
<tr>
<td>All 3 Factors</td>
<td>75% reduction</td>
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HR Black vs White, age, sex adj: 2.04 (1.76-2.37)

Mediation of Racial Difference by other Risk Factors: ARIC, 10-22y F/U

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</tr>
<tr>
<td>Genetic Risk score</td>
<td>9% reduction</td>
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</table>
Race and VTE to this point in the talk

- Black people have higher risk and burden than other groups (higher risk of provoked VTE)

- Risk factors, lifestyle and social factors (weight, income, FVIII) explain 75% of the excess risk in Black people, but 25% is unexplained.

This offers ideas for prevention

- *Is prophylaxis adequate in trauma centers serving poor people?*
- *Is structural racism at play?*
- *Are clinical trials inclusive? Is race reported?*
Are there Race-Specific Risk Factors?
Sickle Cell Trait as a Candidate to Explain Racial Differences in VTE

- ~8% of African-Americans have HbAS
- HbSS and HbAS, are associated with a prothrombotic state

HbSS increases VTE risk, especially PE

Westerman, Am J Hematol 2002
Naik Am J Med 2013

Hypoxia and slow flow

http://www.stemlynsblog.org
## Sickle Cell Trait & VTE: LITE Study

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Sickle Trait</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence per 1000 py</td>
<td>3.1</td>
<td>4.8</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>1.0 (ref)</td>
<td>1.6 (1.0-2.4)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, ancestry

Folsom A. JTH 2015
The level of VTE risk with sickle trait is similar to the risk of OCP or HRT, AND in a population with higher baseline risk and higher obesity prevalence.
## Absolute Risk

LITE Study, 1987-2011

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk</th>
<th>Lifetime Risk at Age 45, %</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>n/a</td>
<td>8.1</td>
<td>1 in 12</td>
</tr>
<tr>
<td>Black Americans</td>
<td>1.6</td>
<td>11.5</td>
<td>1 in 9</td>
</tr>
<tr>
<td>Obese</td>
<td>2.0</td>
<td>10.9</td>
<td>1 in 9</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>5-7</td>
<td>17.1</td>
<td>1 in 6</td>
</tr>
<tr>
<td>Sickle Trait</td>
<td>1.8</td>
<td>18.2</td>
<td>1 in 5</td>
</tr>
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</table>

Bell Am J Med 2016
Risk of VTE with HbAS Plus other Risk Factors

HbAA

HbAS

RR ~2

Obese
Risk of VTE with HbAS Plus other Risk Factors

HbAA

HbAS

HR ~2

Obese with HRT

Obese

RR

0

50

100
Risk of VTE with HbAS Plus other Risk Factors

HbAA

HbAS

Obese with HRT + Surgery
Obese with HRT
Obese

HR ~2

RR

0 50 100
Absolute Risk in a 60 year old ~25% for several weeks
Applications of Emerging Knowledge in Sickle Cell Trait

- Awareness of health risks in carriers
  - Problematic due to low carrier awareness

- Can we act on this in trauma care?
Summary: VTE Disparity in Black People

- VTE more serious and prevalent for Black people
- Might be mediated by
  - Obesity, Lifestyle
  - Socioeconomic factors
  - Structural racism (?)
  - Efficacy of thromboprophylaxis (?)
  - Coagulation factor differences
  - Sickle cell trait
Research to Practice Challenge

Epidemiology Studies

Human Testing

Trials / Pragmatic Trials

Quality / Implementation Science
Research to Practice Challenge

Epidemiology Studies

- Include URM people in trials
- Report results for URM people in observational studies
- Study racial differences in VTE after trauma
- Improve systems of care for VTE prevention and diagnosis in trauma patients in minoritized communities
- Consider unconscious bias in healthcare

Action – what can YOU do?
Summary

- For outstanding clinical care, draw on information from all sources - high quality clinical trials and epidemiology
  - We will never have an RCT for all questions
- Epidemiology and implementation research play important roles
- Great opportunity for the trauma community for new research on race differences / disparities
UVM
Neil Zakai
Elaine Cornell
Christina Evans

LITE
Aaron Folsom
Pamela Lutsey
Wayne Rosamond
Susan Heckbert
Many Students

Funding
NHLBI

@MaryCushmanMD