Effectiveness and Safety of Direct Oral Anticoagulants and Warfarin Among Patients with Sickle Cell Disease: A Retrospective Cohort Study

Megan Roberts, PharmD, BCPS
MUSC Medical Center and South Carolina College of Pharmacy Residency Program Charleston, SC
Disclosure Statement

- No researchers have conflicts of interest to disclose
  - Megan Roberts, PharmD, BCPS
  - Eric Gaskill, PharmD Candidate
  - Nicole Bohm, PharmD, BCPS
  - Brittany Jones, PharmD, BCPS
  - Julie Kanter, M.D.
  - T. Rogers Kyle III, M.D.

- The off-label use of medications will be discussed
Background

Venous thromboembolism (VTE) among patients with Sickle Cell Disease (SCD)

- Compared with non-SCD population
  - Younger age
  - Higher incidence and recurrence
  - Higher mortality
- Attributed to
  - Hypercoaguable state
  - Central venous catheters
  - Frequent hospitalizations and surgeries

Background

- VTE treatment with oral anticoagulants among patients with SCD
  - Warfarin
    - Traditionally used, little evidence
    - Difficulty maintaining INR within therapeutic range
  - Direct Oral Anticoagulants (DOACs): apixaban, dabigatran, edoxaban, and rivaroxaban
    - No studies to date including patients with SCD

Purpose

- To characterize and evaluate the effectiveness and safety of oral anticoagulants for VTE treatment among patients with SCD
## Objectives

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
<th>Additional</th>
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</thead>
<tbody>
<tr>
<td><strong>Effectiveness</strong></td>
<td><strong>Safety</strong></td>
<td><strong>Effectiveness</strong></td>
</tr>
<tr>
<td>Incidence of recurrent VTE</td>
<td>Incidence of major bleeding</td>
<td>Death related to VTE</td>
</tr>
<tr>
<td></td>
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<td>Time of INR within therapeutic range</td>
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</tbody>
</table>
Methods

- IRB-approved, retrospective chart review conducted at an academic medical center and affiliated outpatient provider clinics

Inclusion criteria:
- ≥ 18 years of age
- Diagnosed with SCD with documented phenotype
- Objectively documented VTE
- Documented administration of warfarin or a DOAC
- July 1, 2012 to June 30, 2016

Exclusion criteria:
- Pregnancy
- Indication for anticoagulation other than VTE
- Sickle cell trait
Methods

- Patients identified by the Clinical Data Warehouse based on ICD codes for SCD and VTE and administration of DOAC, warfarin, or anticoagulant reversal agents

- Data collected
  - For 6 months following VTE occurrence
  - Rationale for \( \geq 1 \) anticoagulant during study period

- Statistical analysis
  - Descriptive statistics
## Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Population (n = 37)</th>
<th>DOAC (n = 22)</th>
<th>Warfarin (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (IQR), years</strong></td>
<td>28 (9)</td>
<td>27.5 (8)</td>
<td>33 (10)</td>
</tr>
<tr>
<td><strong>Male, %</strong></td>
<td>46</td>
<td>41</td>
<td>53</td>
</tr>
<tr>
<td><strong>BMI ≥ 40 kg/m², %</strong></td>
<td>8</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td><strong>HbSS phenotype, %</strong></td>
<td>92</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td><strong>Diagnosis, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Extremity DVT</td>
<td>46</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Lower Extremity DVT</td>
<td>13</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>41</td>
<td>41</td>
<td>53</td>
</tr>
<tr>
<td><strong>CVC present, %</strong></td>
<td>78</td>
<td>77</td>
<td>87</td>
</tr>
<tr>
<td><strong>Creatinine clearance &lt; 50 mL/min, %</strong></td>
<td>81</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td><strong>Hepatic impairment, %</strong></td>
<td>3</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

DVT: deep vein thrombosis  
CVC: central venous catheter
Results – Effectiveness and Safety Outcomes

<table>
<thead>
<tr>
<th>Percentage of patients experiencing target outcomes</th>
<th>Population (n = 37)</th>
<th>DOAC (n = 22)</th>
<th>Warfarin (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE recurrence</td>
<td>27</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Death related to VTE</td>
<td>3</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Hospitalizations for VTE complications</td>
<td>41</td>
<td>32</td>
<td>53</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>16</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>35</td>
<td>23</td>
<td>53</td>
</tr>
</tbody>
</table>
## Results – Additional Outcomes

<table>
<thead>
<tr>
<th>Medication related outcomes (%)</th>
<th>Population</th>
<th>DOAC (n = 19)</th>
<th>Warfarin (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appropriate dosing</strong></td>
<td>N/A</td>
<td>84</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Concomitant interacting medications</strong></td>
<td>89 (n = 37)</td>
<td>86 (n = 22)</td>
<td>93 (n = 15)</td>
</tr>
<tr>
<td><strong>Time that INR was within the therapeutic range</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>0 to 39 (n = 15)</td>
</tr>
<tr>
<td><strong>Patients reporting missed anticoagulant doses</strong></td>
<td>57 (n = 30)</td>
<td>50 (n = 16)</td>
<td>64 (n = 14)</td>
</tr>
</tbody>
</table>
Results – Additional Outcomes

Rationale for Receipt of ≥ 1 Anticoagulant During Study Period (n = 12)

- Back Pain: 8%
- Non-adherence: 42%
- New VTE: 50%
- Recurrent VTE: 8%
- Sub-therapeutic INR: 42%
Discussion

- Limitations
  - Retrospective chart review dependent on reliable documentation
  - Small sample size
  - Single center study
  - Emergence of novel DOACs since beginning of study period
  - Inability to account or adjust for prescribing preferences including those based on patient characteristics
Discussion

- **Summary of results**
  - VTE recurrence and safety events were similar between groups
  - Higher incidence than pivotal NOAC VTE trials

- **Future directions**
  - Discussion of findings with providers
  - Ideally, further investigation
    - Intense monitoring of warfarin
    - PD and PK in patients with SCD
      - Dose intensity
    - Larger, multi-site, prospective trial
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