Role of Direct Oral Anticoagulants in the Treatment of Cancer-Associated VTE


Tuesday, November 6, 2018, 12:00PM ET

Guest Discussant: Marc Carrier, MD, MSc, FRCPC

Moderators: Diane Wirth, ANP, CACP; Michael Streiff, MD; Sara Vazquez, PharmD, BCPS, CACP
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Disclosures

• Marc Carrier
  • Pfizer
  • Bayer
  • Leo Pharma
  • Bristol Meyer Squibb

• Diane Wirth
  • Janssen Pharmaceutical
  • Portola Pharmaceutical
Definitions/Abbreviations

• International Society of Thrombosis and Hemostasis (ISTH)
• Scientific and Standardization Committee (SSC)
• Cancer associated Thrombosis (CAT)
• Randomized Clinical Trials (RCT)
• Cancer
  • Dx within previous 6 months, recurrent, regionally advanced, or metastasized, tx within past 6 months or hematological cancer not in remission
• Direct oral anticoagulant (DOAC)
  • Apixaban (Eliquis)
  • Dabigatran (Pradaxa)
  • Edoxaban (Savaysa)
  • Rivaroxaban (Xarelto)
Cancer and clotting

- Risk is much higher for VTE
  - 4-7 fold increase risk of developing VTE
- Challenging to manage
  - bleeding
  - drug interaction
  - compliance with LMWH
  - vitamin K antagonist failures
  - nausea/vomiting with treatments
Factors that contribute to VTE in cancer patients

• Pro-coagulant and inflammatory cytokines
• Immobility and venous external compression
• Vessel damage
  • chemotherapy-induced interleukin
  • tumor necrosis factor
  • indwelling catheters
• Concomitant genetic hyper-coaguable states
• Chemo therapy agents

Cancer with high rates of VTE

- Pancreatic
- Hematologic
- Lung
- GI
- Brain

Review Questions

• What is the role of DOAC’s in cancer associated VTE?
• Which patients have had the best results with DOAC’s?
• Are there patients that LMWH is a safer therapy for?
Study Selection for Review

https://doi.org/10.1016/j.thromres.2018.02.144 A.Li, et al
RCT for DOAC vs LMWH

Hokusai Cancer Study (Raskob) 1046 patients
Edoxaban 60 mg daily or dalteparin 200 IU/KG daily
month 1 then 150 IU/KG month 2-12 (lead in with parenteral)

Select-D (Young) 406 patients
Rivaroxaban 15 mg bid x 21 days then 20 mg daily or
200 IU/KG daily month 1 then 150 IU/KG month 2-6
Forest plots of relative risks (RRs) for pooled outcome comparisons between DOAC and LMWH from randomized controlled trials

(A) VTE recurrence by 6-month

(B) major bleeding by 6-month

https://doi.org/10.1016/j.thromres.2018.02.144. A. Li et al.
Forest plots of relative risks (RRs) for pooled outcome comparisons between DOAC and LMWH from randomized controlled trials

### (C) Clinically Relevant Non-Major Bleeding (CRNMB) by 6-month

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOAC Events</th>
<th>Total</th>
<th>LMWH Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskob 2017</td>
<td>64</td>
<td>522</td>
<td>43</td>
<td>524</td>
<td>57.6%</td>
<td>1.49 [1.04, 2.16]</td>
</tr>
<tr>
<td>Young 2017</td>
<td>25</td>
<td>203</td>
<td>6</td>
<td>203</td>
<td>42.4%</td>
<td>4.17 [1.75, 9.94]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>725</strong></td>
<td></td>
<td><strong>727</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>2.31 [0.85, 6.28]</strong></td>
</tr>
</tbody>
</table>

**Total events**
- 89
- 49

Heterogeneity: $\text{Tau}^2 = 0.42; \text{Chi}^2 = 4.60, \text{df} = 1 (P = 0.03); I^2 = 78\%$

Test for overall effect: $Z = 1.64 (P = 0.10)$

### (D) Overall Mortality by 6-month

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOAC Events</th>
<th>Total</th>
<th>LMWH Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskob 2017</td>
<td>140</td>
<td>522</td>
<td>127</td>
<td>524</td>
<td>69.1%</td>
<td>1.11 [0.90, 1.36]</td>
</tr>
<tr>
<td>Young 2017</td>
<td>48</td>
<td>203</td>
<td>54</td>
<td>203</td>
<td>30.9%</td>
<td>0.89 [0.63, 1.24]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>725</strong></td>
<td></td>
<td><strong>727</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.03 [0.85, 1.26]</strong></td>
</tr>
</tbody>
</table>

**Total events**
- 188
- 181

Heterogeneity: $\text{Tau}^2 = 0.00; \text{Chi}^2 = 1.18, \text{df} = 1 (P = 0.28); I^2 = 15\%$

Test for overall effect: $Z = 0.33 (P = 0.74)$
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>DOAC</th>
<th>LMWH</th>
<th>Endpoints (time)</th>
<th>DOAC</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskol</td>
<td>RCT</td>
<td>Number (follow-up)</td>
<td>522 (12 mo)</td>
<td>524 (12 mo)</td>
<td>VTE (6 mo)</td>
<td>6.5% (45/822)</td>
<td>8.8% (40/452)</td>
</tr>
<tr>
<td>2017 [11]</td>
<td></td>
<td>Patient age, gender</td>
<td>64, 53% male</td>
<td>64, 50% male</td>
<td>MB (6 mo)</td>
<td>0.6% (29/522)</td>
<td>3.2% (17/524)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA type, stage</td>
<td>11% hemi, 53% met</td>
<td>11% hemi, 53% met</td>
<td>CRNMB (6 mo)</td>
<td>12.3% (64/522)</td>
<td>8.8% (43/524)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VTE type, history</td>
<td>32% incidental, 9% hxs</td>
<td>33% incidental, 12% hxs</td>
<td>Death (6 mo)</td>
<td>12.9% (10/222)</td>
<td>24.2% (127/524)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug name (duration)</td>
<td>Edinonan (6.9 mo)</td>
<td>Dalteparin (6.0 mo)</td>
<td>VTE (12 mo)</td>
<td>7.9% (41/522)</td>
<td>13.2% (209/524)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number (follow-up)</td>
<td>203 (6 mo)</td>
<td>203 (6 mo)</td>
<td>MB (12 mo)</td>
<td>6.9% (36/522)</td>
<td>4.0% (11/274)</td>
</tr>
<tr>
<td>2017 [12]</td>
<td>RCT</td>
<td>Patient age, gender</td>
<td>67, 54% male</td>
<td>67, 48% male</td>
<td>CRNMB (12 mo)</td>
<td>14.6% (77/522)</td>
<td>11.1% (59/524)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA type, stage</td>
<td>59% met</td>
<td>59% met</td>
<td>Death (12 mo)</td>
<td>39.5% (206/522)</td>
<td>36.6% (192/524)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VTE type, history</td>
<td>54% incidental</td>
<td>52% incidental</td>
<td>VTE (6 mo)</td>
<td>3.9% (8/203)</td>
<td>0.9% (18/203)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug name (duration)</td>
<td>Rivanol (52% at 6 mo)</td>
<td>Dalteparin (52% at 6 mo)</td>
<td>MB (6 mo)</td>
<td>5.4% (11/203)</td>
<td>3.0% (6/203)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number (follow-up)</td>
<td>146 (12 mo)</td>
<td>223 (12 mo)</td>
<td>CRNMB (6 mo)</td>
<td>12.3% (25/203)</td>
<td>3.0% (6/203)</td>
</tr>
<tr>
<td>2017 [19]</td>
<td>Cohort</td>
<td>Patient age, gender</td>
<td>69, 52% male</td>
<td>68, 47% male</td>
<td>Death (6 mo)</td>
<td>2.0% (40/203)</td>
<td>2.0% (40/203)</td>
</tr>
<tr>
<td></td>
<td>(record)</td>
<td>CA type, stage</td>
<td>8% hemi, 14% GI CA</td>
<td>10% hemi, 29% GI CA</td>
<td>VTE (12 mo)</td>
<td>1.4% (5/146)</td>
<td>1.4% (2/146)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VTE type, history</td>
<td>28% hxs</td>
<td>12% hxs</td>
<td>MB (12 mo)</td>
<td>1.4% (2/146)</td>
<td>1.4% (2/146)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug name (duration)</td>
<td>Rivanol (5.0 mo)</td>
<td>Dalteparin (5.0 mo)</td>
<td>CRNMB (12 mo)</td>
<td>12.3% (25/203)</td>
<td>3.0% (6/203)</td>
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<tr>
<td>2017 [10]</td>
<td>Cohort</td>
<td>Patient age, gender</td>
<td>48 (10.4 mo)</td>
<td>23 (&lt; 6 mo)</td>
<td>NR (14/141)</td>
<td>4.0% (7/146)</td>
<td>34.7% (50/141)</td>
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<tr>
<td></td>
<td>(record)</td>
<td>CA type, stage</td>
<td>62, 50% male</td>
<td>62, 39% male</td>
<td>VTE (12 mo)</td>
<td>2.1% (1/48)</td>
<td>12.0% (3/33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VTE type, history</td>
<td>33% met</td>
<td>70% met</td>
<td>MB (6 mo)</td>
<td>5.3% (3/48)</td>
<td>12.0% (3/33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug name (duration)</td>
<td>Rivanol (9.7 mo)</td>
<td>Enoxaparin (4.5 hr)</td>
<td>NR (14/141)</td>
<td>31.6% (50/141)</td>
<td>34.7% (50/141)</td>
</tr>
<tr>
<td>2017 [20]</td>
<td>Cohort</td>
<td>Patient age, gender</td>
<td>107 (6 mo)</td>
<td>179 (6 mo)</td>
<td>VTE (6 mo)</td>
<td>2.8% (3/107)</td>
<td>6.1% (11/179)</td>
</tr>
<tr>
<td></td>
<td>(record)</td>
<td>CA type, stage</td>
<td>62, 52% male</td>
<td>59, 51% male</td>
<td>MB (6 mo)</td>
<td>2.8% (3/107)</td>
<td>1.1% (2/179)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VTE type, history</td>
<td>20% home, 68% met</td>
<td>20% home, 76% met</td>
<td>CRNMB (6 mo)</td>
<td>3.9% (10/107)</td>
<td>4.5% (9/197)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug name (duration)</td>
<td>Rivanol (5.0 mo)</td>
<td>Dalteparin (5.0 mo)</td>
<td>Death (6 mo)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2017 [21]</td>
<td>Cohort</td>
<td>Patient age, gender</td>
<td>30 (11.6 mo)</td>
<td>123 (11.6 mo)</td>
<td>VTE (12 mo)</td>
<td>6.7% (2/30)</td>
<td>8.3% (10/123)</td>
</tr>
<tr>
<td></td>
<td>(record)</td>
<td>CA type, stage</td>
<td>62, 43% male</td>
<td>58, 44% male</td>
<td>MB (12 mo)</td>
<td>11.3% (3/28)</td>
<td>10.6% (13/123)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VTE type, history</td>
<td>24% home, 31% met</td>
<td>27% home, 54% met</td>
<td>CRNMB (12 mo)</td>
<td>6.7% (2/30)</td>
<td>7.9% (9/123)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug name (duration)</td>
<td>Enoxaparin (NR)</td>
<td>Enoxaparin (NR)</td>
<td>Death (12 mo)</td>
<td>NR</td>
<td>NR</td>
</tr>
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<td>Segmentum</td>
<td>Article (record)</td>
<td>Number (follow-up)</td>
<td>Patient age, gender</td>
<td>CA type, stage</td>
<td>VTE type, history</td>
<td>Drug name (duration)</td>
<td>vTE (to mo)</td>
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<td>2017 [33]</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Phelps</td>
<td>100 (25 mo)</td>
<td>60, 100% female</td>
<td>100% GYN, 35% met</td>
<td>27% hx</td>
<td>Riva, NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2016 [34]</td>
<td>58 overall</td>
<td>32% heme</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Hummert</td>
<td>85 (NR)</td>
<td>65, 54% male</td>
<td>53% met overall</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Rahman</td>
<td>23 (NR)</td>
<td>149 (NR)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Seo</td>
<td>78 (NR)</td>
<td>111 (NR)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Ohlmann</td>
<td>360 (NR)</td>
<td>431 (6.8 mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sheiff</td>
<td>660 (5.6 mo)</td>
<td>707 (5.6 mo)</td>
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</tr>
</tbody>
</table>


https://doi.org/10.1016/j.thromres.2018.02.144. A. Li et al.
The results....

• Over 5000 CAT patients reviewed between RCT and observational studies comparing DOAC/LMWH
  • Efficacy
    • Overall lower rates of recurrence of VTE in DOAC patients (absolute risk -3%, -6% to 0%)
  • Safety
    • Higher risk of major and clinically relevant non major bleeding in DOAC patients (absolute risk +2%, 0%--+4%)
  • Compliance
    • Generally better compliance in DOAC patients 15% in Hokusai-Cancer vs 4% in LMWH group

Shared Decision Making

- Patient preference
- Values
- Concerns
  - Will DOAC interfere with their cancer treatment?
  - Are they more concerned about efficacy or bleeding

Patients highest risk for bleeding on DOAC based on RCT’s and observational studies

- Gastrointestinal cancer
- Genitourinary cancer

https://doi.org/10.1016/j.thromres.2018.02.144. A. Li et al.
Cautions

• No validated bleeding risk tools for cancer patients receiving DOAC’s

• Edoxaban and rivaroxaban are the only two DOAC’s in RCT’s

• Renal function is important in both DOAC and LMWH therapy, there is no reduced dose for DOAC’s for renally impaired VTE treatment
Guidance Statement

• Shared decision making
  • Individualize plan for each patient

• Suggest DOAC’s if the following is true
  • Low bleeding risk
  • No drug-drug interactions

• Suggest LMWH’s if the following is true
  • High bleeding risk
  • Luminal GI cancers
  • GI mucosal abnormalities
  • GU tract cancers
  • Nephrostomy tubes