DOACs in CAT

Fellow: Shweta Jain, MD
Faculty Discussant: David Garcia, MD
Case

• 65 year old post menopausal female
• Left breast lesion Oct 2015 → Biopsy – Invasive ductal carcinoma
• Lumpectomy with SNB- pT1cNo left breast ER/PR +, Her2 -, grade II
  Invasive ductal Ca in Nov 2015
• Oncotype score Low recurrence risk → radiation + Aromatase inhibitor
• PMH: unprovoked VTE x 2 episodes
  – 2007- Left LE DVT
  – 2012 – Left Greater Saphenous vein, B/L segmental lower lobe PE
  – Risk factors: smoking, obese, Varicose veins
  – Negative Hypercoagulability work up
  – Negative family history
• Treatment course: Coumadin x 2 years, “hated it” , no adverse effects, no
  major bleeding. Transitioned to Rivaroxaban in 2014
• Heme Consult for: Keep Rivaroxaban versus LMWH
Talk overview

• CAT scenarios
• Pros to support DOACs use
• Review evidence
  – Dabigatran, Apixaban, Edoxaban, Rivaroxaban
  – Meta-analysis
• Cons against DOAC use
• Summary
CAT scenarios

- Primary prophylaxis
- Symptomatic VTE- acute care, follow up care
- Incidental VTE
- Catheter associated thrombosis
- Recurrent
- Duration- active cancer/thrombogenic therapy vs surveillance/remission
Pros DOACs

- Oral route
- No lab monitoring
- Decreased bleeding rate *
- Similar Efficacy *
Dabigatran

- Time to peak: 1-3 hours
- Half Life: 12-17 hours
- 80% renal clearance
  ( * VTE prevention after ortho surgery)

Dabigatran Efficacy

- **RE-COVER, RE-COVER II**
  - Randomized, double blind
  - Acute symptomatic VTE, n2589 pts
  - Dabigatran 150 mg po BID*
  - c/w warfarin*
  - 6 months
  - VTE recurrence: HR 1.09 (CI 0.76-1.57)
  - Bleeding risk: HR 0.70 (CI 0.61-0.79), Major bleeding HR 0.73 (CI 0.48-1.11)

Schulman et al NEJM 2009;361:2342-52
Schulman et al Circulation 2014;129:764-72
Dabigatran- CAT (Subgroup analysis)

Active cancer at baseline- 7% \((n=357/5107)\)

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Warfarin</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE/VTE related Deaths</td>
<td>5.8% (10/173)</td>
<td>7.4% (12/162)</td>
<td></td>
</tr>
<tr>
<td>Major bleeding*</td>
<td>3.8% (6/159)</td>
<td>4.6% (7/152)</td>
<td>0.60 (CI 0.36-0.99)</td>
</tr>
<tr>
<td>Clinically relevant bleeding**</td>
<td>14.5% (23/159)</td>
<td>13.2% (20/152)</td>
<td>1.12 (CI 0.59-2.13)</td>
</tr>
</tbody>
</table>

*Major bleeding rate in non cancer group (0.8%-- 1.4% respectively)
** Clinically relevant bleeding in non cancer group ( 3.7%-- 7.3% respectively)

Schulman et al ASH abstract 2013 (582)
Dabigatran-Efficacy

• Re-MEDY trial
  – Randomized, double blind
  – Acute VTE-treated successfully for 3 months
  – Duration 6-36 months
  – c/w Warfarin ; c/w placebo
  – Dabigatran 150 mg po BID (n 1430)
  – Recurrent VTE: HR 1.44 ( CI 0.78-2.64)
  – Bleeding : HR 0.71 ( CI 0.61-0.83) , Major bleeding HR 0.52 (CI 0.27- 1.02)

Schulman et al NEJM 2013;368:709-18
Dabigatran- CAT (Subgroup analysis)

Active cancer at baseline- 4.2% ($n=112$)

<table>
<thead>
<tr>
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<th>Dabigatran</th>
<th>Warfarin</th>
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<tbody>
<tr>
<td>Recurrent VTE</td>
<td>2.2% (2)</td>
<td>1.7% (1)</td>
</tr>
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</table>

Schulman et al NEJM 2013;368:709-18
Apixaban

- Time to peak: 1-3 hours
- Half Life: 8-15 hours
- 25% renal clearance
  (* VTE prevention after ortho surgery)

Raghavan et al. Drg Metab Dispos 2009;37:74-81
Apixaban-Efficacy

• AMPLIFY
  – Double blind, Randomized
  – **Acute VTE**
  – Apixaban: 10 mg po BID x 7 days → 5mg po BID
  – c/w warfarin/ENOXAPARIN
  – Duration x 6 months
  – Recurrent VTE: RR 0.84 (CI 0.60-1.18)
  – Major Bleeding: RR 0.31 (CI 0.17-0.55), Bleeding RR 0.44 (CI 0.36-0.55)

Agnelli et al. NEJM 2013;369:799-808
Apixaban-CAT (Subgroup Analysis)

Active cancer 2.7% \( (n=143) \)

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<tr>
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<th>Apixaban</th>
<th>Warfarin</th>
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<tr>
<td>Recurrent VTE</td>
<td>3.7%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>14.9%</td>
<td>27.5%</td>
</tr>
</tbody>
</table>

Agnelli et al. NEJM 2013;369:799-808
Apixaban-Efficacy

ADOPT trial

- c/w enoxaparin 40 mg subcut OD x 6 - 14 days
- 30 days Apixaban (2.5 mg PO BID)
- Acutely medically ill, n 4495
- Primary efficacy outcome: 30 day : VTE/related death: RR 0.87 (CI 0.62- 1.23, p=0.44)
- Major bleeding : RR 2.58 (CI 1.02- 7.24, p =0.04)
- Active cancer : 3.5% and 3% in the treatment and placebo arm respectively

Goldhaber et al NEJM 2011;365:2167-77
Apixaban-CAT

• Phase II, pilot study, Tolerability, ambulatory cancer pts
• Primary Prevention
• Randomized, placebo controlled
• 125 patients
• advanced/metastatic solid organ malignancy, myeloma
• Excluded if survival less than 6 months, ECOG >/=3, h/o DVT/PE, excluded Sunitinib, Sorafenib
• 4 treatment arms: Apixaban 5mg, 10mg, 20 mg daily, or placebo
• Duration-12 weeks

Levine et al J Thromb Haemost. 2012 May;10(5):807-14
Apixaban-CAT

Results: appears tolerable
- Bleeding: major bleeding, CRNM
- No Fatal bleeding
- VTE: symptomatic DVT/PE, A/E
- Arm vein thrombus, catheter related thrombus not included

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<thead>
<tr>
<th></th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CRNM</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
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<tr>
<td>VTE</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
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</table>

Levine et al J Thromb Haemost. 2012 May;10(5):807-14
Edoxaban

- Time to peak: 1-3 hours
- Half Life: 8-10 hours
- 35% renal clearance
- Licensed indications: US- VTE treatment, Nonvalvular atrial fibrillation. (* VTE prevention after ortho surgery-Japan)

Bounameaux et al Drugs 2014;74:1209-31
Edoxaban- EFFICACY

• Hokusai-VTE
  – Randomized, double blind
  – Acute symptomatic DVT, n 8292
  – Initial open label enoxaparin or UFH
  – Edoxaban 60 mg po OD /30 mg po OD
  – c/w warfarin
  – Duration: 3-12 months
  – Recurrent VTE : HR 0.89 (CI 0.70-1.13)
  – Bleeding : HR 0.81 (CI 0.71-0.94), Major bleeding
    HR 0.84 (CI 0.59-1.21)

Hokusai-VTE investigators NEJM 2013;369:1406-15
**Edoxaban- CAT (Subgroup Analysis)**

- Active cancer at baseline: 2.5% (208)

<table>
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<tr>
<th></th>
<th>Endoxaban</th>
<th>Warfarin</th>
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<tbody>
<tr>
<td>Recurrent VTE</td>
<td>3.7%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>18.3%</td>
<td>25.3%</td>
</tr>
</tbody>
</table>

Hokusai-VTE investigators NEJM 2013;369:1406-15
Rivaroxaban

• Time to peak : 2-4 hours
• Half Life : 7-13 hours
• 35 % renal clearance
• Licensed indications: US- VTE treatment, Nonvalvular atrial fibrillation, VTE prevention after ortho surgery)

Rivaroxaban-Efficacy

- Einstein DVT, PE study, extended treatment
- Pooled Analysis: acute symptomatic VTE (DVT and/or PE)
  - Phase III, Randomized, open label
  - N=8282 patients
  - Rivaroxaban: 15 mg po BID x 3 weeks -> 20 mg po OD
  - c/w initial subcut enoxaparin followed by Warfarin
  - Recurrent VTE: HR 0.89 (CI 0.66-1.19)
  - Bleeding: HR 0.93 (CI 0.81-1.06), Major bleeding HR 0.54 (CI 0.37-0.79)

The EINSTEIN investigators NEJM 2010;363:2499-510
The EINSTEIN PE investigators NEJM 2012; 366: 1287-97
Prins et al Thromb J 2013;11:21
**Rivaroxaban-CAT** (Subgroup Analysis)

Active cancer at baseline 5.2% (n=430), diagnosed in 2% (n=167)

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>SOC</th>
<th>HR (CI)</th>
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<tbody>
<tr>
<td>Recurrent VTE</td>
<td>5.1% (16/316)</td>
<td>7.1% (20/281)</td>
<td>0.69 (CI 0.36-1.33)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2.8% (9/316)</td>
<td>5% (14/279)</td>
<td>0.53 (CI 0.23-1.23)</td>
</tr>
</tbody>
</table>

Prins et al Thromb J 2013;11:21
Rivaroxaban-Efficacy

• MAGELLAN Trial
  – Randomized, double blind
  – Hospitalized medically ill, n = 8101
  – Rivaroxaban: 2.5 mg po BID X 35 days
  – c/w Enoxaparin 40 mg subcut daily x 10 days
  – Primary Efficacy outcome: VTE /VTE related death:
    • Day 10 : RR 0.97 ( CI 0.71- 1.31, p 0.003)
    • Day 35 : RR 0.77 ( CI 0.62-0.96, p 0.02)
  – Bleeding rate :
    • Day 1-10: RR 2.3 ( CI 1.63- 3.17, p <0.001)
    • Day 1-35: RR 2.5 ( CI 1.85- 3.25, p <0.001)
Rivaroxaban - CAT (Subgroup Analysis)

Active cancer at baseline 7.3% (n=592)

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Enoxaparin</th>
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<tbody>
<tr>
<td>VTE/VTE related death</td>
<td>9.9%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>5.4%</td>
<td>1.7%</td>
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Meta-analysis

• Generalizable results to patients with cancer

• Inclusion criteria
  – Phase III or phase II
  – c/w VKA
  – Active cancer
  – VTE recurrence and bleeding assessed

• 6 studies included
  – Recover I II – Dabigatran, Einstein DVT PE – Rivaroxaban, Amplify- Apixaban, Hokusai et al-
  – Edoxaban, Einstein DVT PE – Rivaroxaban,

VTE Recurrence

VTE recurrence OR 0.63 (CI 0.37 -1.10)

Bleeding

Major Bleeding

OR 0.77 (CI 0.41 - 1.44)

CR Bleeding

OR 0.55 (CI 0.62 – 1.18)

“Cancer patients”

- CLOT trial Dalteparin to VKA in cancer patients. 9% VTE recurrence in Dalteparin vs 17% in VKA—46% time spent in therapeutic range

Lee et al NEJM 2003 2003 Jul 10;349(2):
Recurrent VTE rates in Cancer patients on VKA:

How do the Subgroups of DOAC Registration Trials Compare to previous rates?

<table>
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<th>Recurrent VTE (in VKA-treated patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dedicated RCTs (LMWH comparator)</td>
<td>11.6% (84 of 722)</td>
</tr>
<tr>
<td>Subgroups of DOAC trials</td>
<td>6% (32 of 537)</td>
</tr>
</tbody>
</table>

Data derived from: Vedovati et al. Chest 2015; 147(2):475-83
Lee et al. JAMA 2015;314(7): 677-686
Evidence Review

- VTE recurrence - Compared with VKA - non inferior
- Bleeding - Compared with VKA - ? Better
- No comparator with the SOC- Low Molecular Weight Heparin
Cons

- Randomized Trial Evidence c/w LMWH
- Renal dysfunction
- Liver dysfunction
- Unpredictable clinical course
- CNS metastasis
- Surgical/interventions
- Drug interactions
- Oral route- Nausea/vomiting/Diarrea
Summary

• Clinical Efficacy data
• On going trials
• Trial here: Edoxaban
  – Dalteparin vs Edoxaban
  – 1: 1 Randomization
Thank you