NEW ORAL ANTICOAGULANTS IN SPECIAL POPULATIONS: OBESITY, RENAL FAILURE, CANCER, AND THROMBOPHILIA

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NEW ORAL ANTICOAGULANTS

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>DTI</td>
<td>antiXa</td>
<td>antiXa</td>
<td>Anti Xa</td>
</tr>
<tr>
<td>Renal metabolism</td>
<td>80%</td>
<td>30-60%</td>
<td>25%</td>
<td>50%</td>
</tr>
</tbody>
</table>

New Oral Anticoagulants

Steps In Coagulation | Coagulation Pathway | Inhibitory Drugs
--- | --- | ---
Initiation | TF/VIIa | 
Propagation | X | IX | VIIIa | IXa |
| Xa | Rivaroxaban | Apixaban | Edoxaban |
| Fibrinogen | H | Ha | Dabigatran |

Fibrinogen → Fibrin

American Heart Association
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### Key Differences VTE Treatment

<table>
<thead>
<tr>
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<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral therapy needed initially?</td>
<td>yes, 5-10 days</td>
<td>no</td>
<td>no</td>
<td>yes, at least 5 days</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>BID</td>
<td>BID for 1st 21 days then QD</td>
<td>BID</td>
<td>QD</td>
</tr>
<tr>
<td>Bleeding risk vs warfarin</td>
<td>same</td>
<td>lower</td>
<td>lower</td>
<td>lower (CRNM)</td>
</tr>
</tbody>
</table>

### New Oral Anticoagulants v Warfarin AFIB

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ stroke</td>
<td>X (ischemic and hemorrhagic)</td>
<td>→</td>
<td>X (hemorrhagic)</td>
<td>→</td>
</tr>
<tr>
<td>↓ INTRACRANIAL BLEED</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>↓ MORTALITY</td>
<td>X</td>
<td>X</td>
<td>X**</td>
<td>X</td>
</tr>
<tr>
<td>BLEEDING</td>
<td>↑ GI bleeding</td>
<td>↑ GI bleeding</td>
<td>any cause</td>
<td>↓</td>
</tr>
<tr>
<td>DRUG INTERACTIONS</td>
<td>Least-pGP</td>
<td>pGp &amp; CYP3A4</td>
<td>CYP 3A4</td>
<td>P-Gp</td>
</tr>
<tr>
<td>NUISANCE Side effects</td>
<td>10-20% dyspepsia</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>DOSING</td>
<td>BID</td>
<td>QD</td>
<td>BID</td>
<td>QD</td>
</tr>
<tr>
<td>METABOLISM</td>
<td>80% RENAL</td>
<td>60% RENAL</td>
<td>25% RENAL</td>
<td>50%</td>
</tr>
</tbody>
</table>

### Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants

Dabigatran, Rivaroxaban, Apixaban, Edoxaban vs. Warfarin in AF patients

<table>
<thead>
<tr>
<th>NOAC (events)</th>
<th>Warfarin (events)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOCOP</td>
<td>124/4076</td>
<td>18/9,022</td>
</tr>
<tr>
<td>ROCKETAF</td>
<td>249/7,081</td>
<td>267/7,980</td>
</tr>
<tr>
<td>AIREST!</td>
<td>231/9,320</td>
<td>259/9,081</td>
</tr>
<tr>
<td>ENGAGE-AF-TIMI48</td>
<td>356/7,095</td>
<td>1,107/7,175</td>
</tr>
</tbody>
</table>

Combined (random) | 510/9,514 | 1,317/7,975 | 0.33 (0.15-0.75) | 0.001 |

IS THIS PATIENT A GOOD CANDIDATE FOR A NOAC?

55 YEAR OLD OBESE MAN (160 KG) WITH UNPROVOKED PE

A. Yes  
B. No  
C. I have no idea, that is why I stayed for this talk

58%  18%  24%

NOACS IN OBESITY

<table>
<thead>
<tr>
<th></th>
<th>Prescribing information</th>
<th>AFIB Clinical trials</th>
<th>VTE clinical trials</th>
<th>In practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riva</td>
<td>&gt;120 kg did not influence rivaroxaban exposure</td>
<td>2035 pts &gt; 90 kg 2.44% vs 2.33% (ns)</td>
<td>EINSTEIN DVT/PE safety &amp; efficacy same irrespective of body weight (491 pts &gt; 90kg)</td>
<td>Very little data available for patients &lt; 40 kg and &gt; 120 kg</td>
</tr>
<tr>
<td>Dabi</td>
<td>No mention in prescribing info</td>
<td>2.46% v 2.35% (ns)</td>
<td>502 pts &gt; 100kg 4.4% vs 3.5% (ns)</td>
<td>Same as above</td>
</tr>
<tr>
<td>Apix</td>
<td>No subgroup analysis in obesity</td>
<td>Unpublished subgroup analysis 10-mg dose apixaban 20% ↓ peak if &gt;120 kg.</td>
<td>Same as above</td>
<td></td>
</tr>
</tbody>
</table>

ARE THESE PATIENTS GOOD CANDIDATES FOR A NOAC?

- 55 year old obese man (160 kg) with unprovoked PE
  - I generally do not use NOACs in these patients due to lack of data and inability to confirm therapeutic levels
- 65 year old man with stage IV lung cancer undergoing chemotherapy with acute PE
- 65 year old man with ESRD and AFIB CHAdS2=4
- 30 year old woman with lupus and APLS with history of recurrent VTE currently on warfarin

IS THIS PATIENT A GOOD CANDIDATE FOR A NOAC

30 YEAR OLD WOMAN WITH LUPUS AND APLS WITH HISTORY OF RECURRENT VTE CURRENTLY ON WARFARIN

A. a) Yes  
B. b) No  
C. c) Can I call a consult?

38%  27%  35%
NOACS IN THROMBOPHILIA

- The good news—we don’t test much for these disorders now
- The bad news—we don’t know if NOACS will perform favorably in these patients

ARE THESE PATIENTS GOOD CANDIDATES FOR A NOAC?

- 65 year old man with stage IV lung cancer undergoing chemotherapy with acute PE
- 30 year old woman with lupus and APLS with history of recurrent VTE currently on warfarin
  - I do not use NOACS in patients with APLS in general, pending results of ongoing trial (RAPS). I do use in patients with mild thrombophilia
- 65 year old man with ESRD on HD, AFIB CHADS2=4
- 55 year old obese man (160 kg) with unprovoked PE

IS THIS PATIENT A GOOD CANDIDATE FOR A NOAC?

65 YO MAN WITH ESRD ON HD WITH AFIB CHADS2=4 (HTN CVA DM)

A. Yes
B. No
C. Is maybe an option?

35% 41% 24%
### ARE THESE PATIENTS CANDIDATE FOR NOACS?

- **65 year old man with stage IV lung cancer undergoing chemotherapy with acute PE**
  - NOACS: **yes**
  - NOACS is not recommended in patients with active cancer unless there is a clear indication (e.g., recurrent VTE).

- **30 year old woman with lupus and APLS with history of recurrent VTE on warfarin**
  - NOACS: **yes**
  - NOACS offer improved efficacy compared to warfarin.

- **65 year old man with ESRD on HD, AFIB, CHADS2=4**
  - NOACS: **no**
  - NOACS are contraindicated in patients with ESRD.

- **55 year old obese man (160 kg) with unprovoked PE**
  - NOACS: **yes**
  - NOACS are generally recommended for patients with unprovoked PE.

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### IS THIS PATIENT A CANDIDATE FOR A NOAC?

**65 YEAR OLD MAN WITH STAGE IV LUNG CANCER UNDERGOING CHEMOTHERAPY WITH ACUTE PE**

- **A.** yes
- **B.** no
- **C.** How many more of these questions do I have to answer?

![Graph showing 62% yes, 32% no, 6% unable to answer]

**65 YEAR OLD MAN WITH STAGE IV LUNG CANCER UNDERGOING CHEMOTHERAPY WITH ACUTE PE**

- **A.** yes
- **B.** no
- **C.** How many more of these questions do I have to answer?

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### NOACS V WARFARIN IN CANCER

#### VTE
- Active cancer excluded small #s (2.5-6%)
- Subgroup analyses—no sig Δ in rates recurrent VTE, but small #s

#### AFIB
- Life expectancy had to be 3,2 or 1 years—most pts with advanced cancer excluded (dabi/riva/apix)

**LMWH is the preferred agent in cancer related VTE**
- **Concerns in cancer patients**
  - Fluctuating renal function
  - Thrombocytopenia
  - Many chemotherapeutic agents are pgp1 and or CYP 3A4 inhibitors or inducers
NOACS FOR VTE IN CANCER

Helle et al J Thromb Haemost 2014

ARE THESE PATIENTS CANDIDATE FOR NOACS?

- 65 year old man with ESRD on HD, AFib CHADS2=4
- 30 year old woman with lupus and APLS with history of recurrent VTE on warfarin
- 55 year old obese man (160 kg) with unprovoked PE
- 65 year old man with stage IV lung cancer undergoing chemotherapy with acute PE
  - LMWH is preferred agent for cancer associated VTE. Expert recommendations are NOT to use NOACs in such patients due to lack of data. RCTs ongoing. I use in lieu of warfarin in select patients who refuse LMWH.

CAUTION ADVISED
I AVOID USE PENDING DATA +/- RELIABLE MONITORING

- GFR < 30 ml/min
- Active cancer-LMWH preferred
- BMI > 40 or wt > 140 kg
- Sick inpatient possibly needing interventions
- Warfarin failure *
- Severe thrombophilia (APLS, AT protein C/S)*
- Noncompliant patients