Novel Anticoagulants: Emerging Evidence
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Genesis Care

Topics:
- NOAC – Novel Oral Anti Coagulant
  - NO
  - Non Vit K Oral Anti Coagulant
- DOAC – Direct Oral Anti Coagulant

Evidence vs Eminence Based??
- Is everything I’m going to tell you correct?
  - YES!!! I’m a Cardiologist, I can’t be wrong!
- Will everyone else do exactly the same as me?
  - NO!! But they’re Cardiologists too so they can’t be wrong either!
- Why do we differ??
  - Lack of evidence – eg “Triple Therapy”
  - “Wiggle Room” within available knowledge.

Role of DOACs

- NOVOTEL (21)
  - Multivariate, randomized, double blind, active control, parallel treatment,
    non-inferiority comparison
  - Patients with AF and CHA2DS2-VASc scores 1-6: DOAC (X) vs vitamin K antagonist
  - Apixaban vs Placebo
  - Median follow-up: 2 years
  - No significant difference in outcomes

- ROCKET (60)
  - Multivariate, randomized, double blind, active control, parallel treatment,
    non-inferiority comparison
  - Age ≤ 75 yrs with AF and CHA2DS2-VASc scores 1-6
  - Rivaroxaban vs Placebo
  - Median follow-up: 2 years
  - No significant difference in outcomes

- RE-LY (21)
  - Multivariate, randomized, double blind, active control, parallel treatment,
    non-inferiority comparison
  - Age ≤ 75 yrs with AF and CHA2DS2-VASc scores 1-6
  - Warfarin vs Placebo
  - Median follow-up: 2 years
  - No significant difference in outcomes

Guidelines for Anticoagulation

Valvular Atrial Fibrillation:
- Oral anticoagulant
- Assess bleeding risk (HAS-BLED score): consider patient values/preferences
- NOAC: rivaroxaban, dabigatran, apixaban
- Vitamin K antagonist

Non-valvular atrial fibrillation:
- < 65 years and lone AF including women
- Stroke risk assessment using CHA2DS2-VASc
- Oral anticoagulant
- Assess bleeding risk (HAS-BLED score): consider patient values/preferences
- NOAC: rivaroxaban, dabigatran, apixaban
- Vitamin K antagonist

What is VALVULAR AF?
Real Issue with DOACs

- COMPLIANCE!!!
- Patient misunderstanding of bleeding risks
- Doctor misunderstanding of bleeding risks

Method of Action:

- Warfarin
- Dabigatran 150mg
- Dabigatran 110mg
- Apixaban 5mg
- Apixaban 2.5mg
- Rivaroxaban 20mg
- Rivaroxaban 15mg

Implications for each choice

- Monitoring:
  - Warfarin: REQUIRED
  - Warfarin: POSSIBLE
- Renal Excretion:
  - Warfarin: 0%
  - Dabigatran: 80%
  - Apixaban: 27%
  - Rivaroxaban: 66%
- Half Life:
  - Dabigatran: 36 hrs
  - Apixaban: 11-13 hrs
- Monitoring POSSIBLE:
  - Warfarin: YES
  - Dabigatran: YES
  - Apixaban: NO
  - Rivaroxaban: YES
- Renal Imp.
  - Dabigatran: 13-23 hrs
  - Apixaban: 11-13 hrs
- Peak: Trough
  - Warfarin: 2:1
  - Dabigatran: 2:1
  - Apixaban: 8:1
- CYP3A4
  - Warfarin: YES
  - Dabigatran: NO
  - Apixaban: YES
  - Rivaroxaban: YES
- Drug Interactions
  - Warfarin: YES
  - Dabigatran: Limited
  - Apixaban: Limited
  - Rivaroxaban: Limited
- Interaction Examples
  - Food: Verapamil
  - Alcohol: Amiodarone
  - Meds: Rifampicin, Ketoconazole, Clarithromycin
- Dosing
  - Warfarin: SD, BD with or without food
  - Dabigatran: BD without food
  - Apixaban: SD without food
  - Rivaroxaban: SD without food
- Dialysable
  - Warfarin: NO
  - Dabigatran: YES
  - Apixaban: NO
  - Rivaroxaban: NO
- Antidote Available
  - Warfarin: VitK
  - Dabigatran: In development
  - Apixaban: In development
  - Rivaroxaban: In development

Actual Bleeding Outcomes vs Warfarin

Most major bleeding events managed with supportive care only

- Dabigatran 1.6 nights in ICU
- Warfarin 2.7 nights in ICU
- 30-day mortality 9.1%
- Plasma transfusion more frequent
- 30-day mortality 13%

Actual bleeding outcomes vs Warfarin

*pooled odds ratio for 30 day mortality 0.66 (95% confidence interval, 0.44 – 1.00; P =0.051).

Most major bleeding events managed with supportive care only

Stop NOAC + Measure NOAC Anticoagulant Effect

aPTT TT PT antifxa

Significant Anticoagulant Effect:
Maintain BP + urine output
Control Bleeding
Transfusion support

aPTT TT PT antifxa

NOAC level LOW or ABSENT
Proceed to surgery

Discuss if surgery can be delayed?

YES for >12hrs:
Refer to Elective Surgery Strategy
NO – IMMEDIATE SURGERY REQUIRED:
Discuss with Haematology to consider Haemostatic Agent
aPCC (FEIBA) or 3F-PCC (Prothromboplastin-VF)
Bleeding Management – EHRA Guidelines Europace
doi:10.1093/europace/euv309

Table 3: Possible measures to take in case of bleeding

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>Dabigatran, Idarucizumab, Andexanet alfa, Ciraparantag</td>
</tr>
</tbody>
</table>

**NOAC reversal agents: stages of development**

<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Target</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab</td>
<td>Dabigatran</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Andexanet alfa</td>
<td>FXa inhibitors</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ciraparantag</td>
<td>Universal</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

*Dabigatran levels before and after treatment with idarucizumab*

- **Group A (n=51)**
  - Initial level:
    - 150 mg: 145 ng/mL
    - 110 mg: 120 ng/mL
  - Final level:
    - 150 mg: 110 ng/mL
    - 110 mg: 75 ng/mL

- **Group B (n=30)**
  - Initial level:
    - 150 mg: 145 ng/mL
    - 110 mg: 120 ng/mL
  - Final level:
    - 150 mg: 110 ng/mL
    - 110 mg: 75 ng/mL

Mortality rate (%)

- **Warfarin**: 10%
- **Dabigatran 150 mg and 110 mg, combined from all studies**: 5%

Dabigatran associated with improved mortality outcomes vs warfarin during 30 days after major bleeding

- Dabigatran 150 mg and 110 mg
- Warfarin

Combined data from dabigatran 150 mg and 110 mg treated patients in RE-LY®, RE-COVER™, RE-COVER™ II, RE-MODY™, and RE-SONATE™. Only first major bleed included; analysis not adjusted for covariates.

RESULTS

- Renal function declined over time in all treatment groups.
- After 30 months, average decline was significantly greater in the warfarin group than in either Dabigatran group.
- From 18 months onward, patients were less likely to experience renal function decline (>25%) on Dabigatran.
- Poor INR control (TThR >65%) exhibited faster renal function decline.
- Prior warfarin use and Type 2 Diabetes was associated with more pronounced renal function decline.

Anticoagulation post AF Ablation

- Observational work suggests lower stroke risks post ablation
  - 0.8 vs 5.4% at 47 months (Lin et al. Europace 2013: 15:676)
- Not assessed in randomised fashion
- In patients with a CHADS-VASc ≥ 1 long term anticoagulation should be continued irrespective of ablation outcome.
- In CHADS-VASc 0 patients, 3 months of anti-coagulation is minimum post ablation, after this increased bleeding risk may cancel out stroke risk (Noseworth et al. J Am Heart Assoc 2015;4)
Perioperative Discontinuation

<table>
<thead>
<tr>
<th>Drug (dosing)</th>
<th>Renal function</th>
<th>Low bleeding risk surgery (0-1 day half-life between last dose and surgery)</th>
<th>High bleeding risk surgery (0-1 day half-life between last dose and surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>Low bleeding risk surgery (0-1 day half-life between last dose and surgery)</td>
<td>High bleeding risk surgery (0-1 day half-life between last dose and surgery)</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td>Low bleeding risk surgery (0-1 day half-life between last dose and surgery)</td>
<td>High bleeding risk surgery (0-1 day half-life between last dose and surgery)</td>
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<tr>
<td>Clopidogrel</td>
<td></td>
<td>Low bleeding risk surgery (0-1 day half-life between last dose and surgery)</td>
<td>High bleeding risk surgery (0-1 day half-life between last dose and surgery)</td>
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<tr>
<td>Aspirin</td>
<td></td>
<td>Low bleeding risk surgery (0-1 day half-life between last dose and surgery)</td>
<td>High bleeding risk surgery (0-1 day half-life between last dose and surgery)</td>
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<tr>
<td>Rivaroxaban</td>
<td></td>
<td>Low bleeding risk surgery (0-1 day half-life between last dose and surgery)</td>
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</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td>Low bleeding risk surgery (0-1 day half-life between last dose and surgery)</td>
<td>High bleeding risk surgery (0-1 day half-life between last dose and surgery)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
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Table 2: Perioperative interruption of oral anticoagulants: a suggested management approach

For Warfarin, WOEST trial showed Warfarin + Clopidogrel performed better than Triple Therapy
Still under investigation for DOACs
- RE-DUAL
- PIONEER-AF-PCI
We know that DAPT and Rivaroxaban reduces MACE but increases bleeding (2.1 vs 0.6%) from ATLAS-ACS TIMI 51
- This was on doses lower than for AF (2.5 and 5mg BD)
APPRAISE-2 with Apixaban showed increased bleeding at 1.3% vs 0.5% for placebo

“Triple Therapy”
- For Warfarin, WOEST trial showed Warfarin + Clopidogrel performed better than Triple Therapy
- Still under investigation for DOACs
  - RE-DUAL
  - PIONEER-AF-PCI
- We know that DAPT and Rivaroxaban reduces MACE but increases bleeding (2.1 vs 0.6%) from ATLAS-ACS TIMI 51
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2011 Consensus Statement for Warfarin (USA)

J Am Coll Cardiol. 2014;64(21):2246-2280. doi:10.1016/j.jacc.2014.03.021

EHRA Guidelines for Triple Therapy
doi:10.1093/eurheartj/euv309

Which NOAC??
- Initially all thought to be relatively equal
  - Differences in trial design and numbers may explain the differences in initial results
- Few direct comparisons
  - Some retrospective analyses appear equal
  - Recently JAMA internal Medicine and JACC suggest more bleeding with Rivaroxaban
    - But retrospective propensity matched controls not randomised
    - Dabigatran and Apixaban appear equal
  - Suggesting dosing is more important than mechanism (Direct Thrombin vs Xa inhibition)
    - JACC 2016; (Vol 67) Issue 13
    - JAMA internal medicine Online October 3
  - Daily dosing of importance in adherence
Summary

- NOACs are safe and well studied
  - Lower bleeding rates and greater predictability vs Warfarin

- Unknowns are being assessed
  - Which NOAC – early signs are BD dosing may be preferable
    - Similar stroke reduction, greater bleeding
    - No randomised studies
  - Triple Therapy

- The age of Reversal Agents is upon us
  - In most clinical scenarios they will not be necessary
  - Where used the initial antidotes are highly effective