The future of anticoagulation

*lessons learned from vitamin K antagonists*

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A recent Clinical Case

• 84 year old lady admitted at the department of Internal medicine with pneumonia and congestive heart failure (treated with amoxycillin, furosemide, etc)
• Atrial flutter was recorded and the consulting cardiologist recommended rivaroxaban (15 mg)
• The kreatinin clearance was 30 ml/min; the next few days it was 22 and 20 ml/min
What would you do?

• Follow this advice?
• How to proceed
• Upon discharge: what kind of follow up?
NOACs and the revolution in anticoagulation

- New compounds welcome
- RCT’s show good profiles of NOAC versus vitamin K antagonists (VKA)
- Switch towards simple and practical therapy is appealing to physicians and patients alike
- What will this bring along?
• Are we willing to proceed towards *unmonitored* anticoagulant therapy?
• Prevention of other CV diseases like diabetes, hypertension and dyslipidemia require some form of monitoring

Summary annual reports FNT

Dutch Federation of Anticoagulation Clinics
General AC clinic data 2013

- 58 AC clinics:
  - 460,000 patients
  - >6,0 million INR’s
  - 40,3% blood collected at home
  - 81,1% acenocoumarol (8-97)
The Hague, 1952
Current anticoagulation practice

• Large population with AF, 50% > 75 years
• INR adjusted VKA (2.5-3.5); therapy is monitored, individually
• Side effects (bleeding) recorded
• Of course VKA are nuisance drugs!
• Contact with patients!
So why is this relevant?

• The existing AC network takes on responsibility for case management (on VKA)
• *With NOAC, specialists need to assume the case management role*
• With VKA, there were already (avoidable?) bleeding problems: *mainly due to lack of integrated care*
**HARM (Hospital Admissions Related to Medication)**

<table>
<thead>
<tr>
<th>Reason for Admission</th>
<th>Preventable Admissions, No. (%)</th>
<th>Associated Drugs (No. of Admissions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI tract bleeding</td>
<td>48 (14.5)</td>
<td>Antiplatelets (34), NSAIDs (14), anticoagulants (12), oral corticosteroids (4)</td>
</tr>
<tr>
<td>GI tract symptoms (eg, diarrhea, constipation)</td>
<td>22 (6.6)</td>
<td>Oral antidiabetics (4), laxatives (4), diuretics (4), opiates (3), loperamide (3), statins (3), antibacterial drugs (3)</td>
</tr>
<tr>
<td>Circulatory system: cardiovascular symptoms (eg, dysrhythmias, heart failure)</td>
<td>35 (10.5)</td>
<td>β-Blockers (15), drugs affecting the RAAS (9), calcium antagonist (9), diuretics (9), anticoagulants (7)</td>
</tr>
<tr>
<td>Respiratory symptoms (eg, dyspnea)</td>
<td>26 (7.8)</td>
<td>Diuretics (12), respiratory drugs (6), β-blockers (6), NSAIDs (5)</td>
</tr>
<tr>
<td>Endocrine system: hypoglycemia or hyperglycemia</td>
<td>20 (6.0)</td>
<td>Insulin (18), oral antidiabetics (12), corticosteroids (3), diuretics (3)</td>
</tr>
</tbody>
</table>

Abbreviations: GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin angiotensin aldosterone system.

*An admission can be associated with more than 1 drug and is then mentioned more than once in the list.*
National Standard for Integrated Anticoagulation Care

Landelijke Standaard Ketenzorg Antistolling

voor de eerste- en tweedelijnszorg

FNT, NVK, NIV, NMT, NHG, NVN, RVA, KNMP, NVZA, NVvC, NVvH, Verenso, De Hart & Vaatgroep

Projectrapportage in opdracht van het
Ministerie voor Volksgezondheid, Welzijn en Sport
Organizes AC care in an integrated manner; Patient in charge (central position) 
AC clinic= case manager 
Caretakers communicate!
Next step: patients on any kind of antithrombotic treatment is part of an integrated care chain.
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Landelijke Standaard Ketenzorg Antistolling
voor de eerste- en tweedelijnszorg
versie 2
Non vitamin K dependent oral anticoagulants

- rivaroxaban
- apixaban
- dabigatran
NOACs: unanswered questions

• Fixed dose “dogma”; no more monitoring necessary?
• Adherence issues in uncontrolled medication
• (how to monitor, reversal, thrombolysis, after recent stroke; when to resume; after ICH: when to resume; safe in multimorbid geriatric patients; is there a “therapeutic range”? Long term safety; Hankey, Thromb Haemost 2014; 111: 808 )
Why a fixed dose?

- To get rid of monitoring
- No biochemical basis
- Different with aspirin
Does fixed dose work?

- For VKA it failed
- Surprisingly: for NOACs, it works on average
- Larger therapeutic window, stable kinetics
- Nevertheless: interindividual variation; extreme concentrations will occur
Does one size fit all?
FU via anticoagulation clinic

Observational “real life” study

ten Cate-Hoek et al, unpublished
Rivaroxaban

Levels_Riva20mg

N=44

Median peak (IQR)
Timing and observed data

<table>
<thead>
<tr>
<th>Timing</th>
<th>Plasma levels Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evening n= 14</td>
<td>148(89-197)</td>
</tr>
<tr>
<td>Morning n= 30</td>
<td>194(76-347)</td>
</tr>
</tbody>
</table>

Blood sampling between 9.00 – 11.00 am
Dabigatran

Levels_Dabigatran150mg

Median peak (IQR)
## Published plasma concentrations

<table>
<thead>
<tr>
<th>Drug</th>
<th>C peak (range)</th>
<th>C trough (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 20 mg od</td>
<td>215 ng/mL (22-535)</td>
<td>32 ng/mL (6-239)</td>
</tr>
<tr>
<td>Dabigatran 150 mg bid</td>
<td>175 ng/mL (117-275)</td>
<td>91 ng/ml (61-143)</td>
</tr>
</tbody>
</table>

Peak 2 hours after ingestion, troughs 24 and 12 hours respectively

Levels per patient over time

Levels_Rivaroxaban N=44
<1 month
1 month
3 months
6 months
12 months

0
200
400
600
Levels_Rivaroxaban ng/ml

Rivaroxaban 20 mg
Levels per patient over time

Dabigatran 150 mg

Levels _Dabigatran ng/ml

<1 month 1 month 3 months 6 months
Figure 2 Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration of Dabigatran Calculated for 72-year-old male atrial fibrillation patient with prior stroke and diabetes. Lines and boxes at the top of the panel in...
Levels & Patient characteristics

◆ Long-term FU RE-LY, 9183 pt, 112 isch. stroke (1.3%), 323 major bleed (3.8%)

◆ IS inversely related to trough (p=0.045), age and previous stroke (p<0.0001)

◆ Major bleed related to dabigatran overexposure (p<0.0001), age (p<0.0001) and ASA use (p<0.003) and diabetes (p<0.018)
Edoxaban trough & outcomes

Figure: Linear plot of events over 3 years across continuous Edoxaban Concentration (at Day 29)
Predicted probabilities - PRE DOSE - After applying exclusion criteria (cut at PK <=150)

- Major Bleed
- Stroke or SEE
- ICH

Engage AF, TIMI 48, presented at ESC 2014
Tailoring NOAC therapy?

• Select an anticoagulant (VKA or NOAC) on the basis of clinical criteria (age, morbidity, eg renal function; “frailty” (what is more important: robust efficacy or safety??), estimated adherence

• In case of NOAC, check PK in individual patient; at least trough (and peak?) value

• Consider switching therapy based on plasma activity (ideally knowing for all NOACS the therapeutic window)
Evidence network for all-cause stroke or systemic embolism.

Cameron C et al. BMJ Open 2014;4:e004301
OR for all-cause stroke or systemic embolism (A) and major bleeding (B) in Bayesian network meta-analysis versus standard adjusted dose VKA. CrI, credible interval; VKA, vitamin K antagonist.

Cameron C et al. BMJ Open 2014;4:e004301
Adherence issues in uncontrolled medication

- CV medication: overall poor adherence
- What are the risk factors?
- NOACs: limited data

**Adherence** to medication: proper intake of medication when properly described

**Maintenance**: the extent to which a patient continues good health practices without professional supervision

**Compliance**: the extent to which a patient implements a prescribed remedy
Many patients stop taking their medications
Adherence rates plummet in just a few months

<table>
<thead>
<tr>
<th>Treatment area</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>60%</td>
<td>52%</td>
<td>41%</td>
</tr>
<tr>
<td>Diabetes (type 2)</td>
<td>53%</td>
<td>43%</td>
<td>41%</td>
</tr>
<tr>
<td>Obesity</td>
<td>48%</td>
<td>41%</td>
<td>38%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47%</td>
<td>43%</td>
<td>35%</td>
</tr>
<tr>
<td>Depression</td>
<td>34%</td>
<td>20%</td>
<td>10%</td>
</tr>
</tbody>
</table>

By the end of the first year of treatment, 50 to 90% of patients stop taking their prescribed therapies.

* Adherence rate ranges were averaged.  
Source: Various sources, A.T. Kearney analysis.
Reasons for non-adherence

• Forgetfulness: 30%
• Other priorities 16%
• Personal decision to omit doses 11%
• Misunderstanding 9%
• Emotional factors 7%
• No reason provided ±27%

survey, Cramer et al, Heart 2002
“Adherence is the extent to which a person’s behavior [in] taking medication... corresponds with agreed recommendations from a health care provider”

(World Health Organization, 2003)

Adherence is a multidimensional phenomenon determined by the interplay of five sets of factors, termed “dimensions” by the World Health Organization.
Recent data on adherence to NOAC (dabigatran)

- 70 pts, New Zealand; 24% discontinued *(Michel et al, Heart Lung Circ 2013)*
- 102 pts, New Zealand; 30% after 9 mo *(Thorne et al, Int Med J 2014)*
- 10,664 users; 25.7% discontinued < 6 mo; of those, a third switched to warfarin *(Jacevicius et al, abstract ASH 2013)*
• 17,691 pts: 39.9% were non persistent and the majority of those were not treated with warfarin upon discontinuation! *(Tsai et al, Am J Managed Care 2013)*

• 6256 cohort; 81% had a gap in therapy with a median of 2 gap days. Lower adherence was associated with a higher risk of death/stroke (HR 1.20 per 0.1 unit lower PDC, and HR 1.13 for stroke only) *(Shore et al, abstract ASH 2013)*
A possible way to go in NOAC management

• Structured, integrated care
• Frequent patient contacts
• Education, check on side effects, complications, proper drug intake
• Check NOAC activity level, renal (and liver?) function at least annually (first 2 years per 6 months)
• Expert centres for guidance, training, complex patient consultation etc
Thanks to: Martin Schalij, Eric Dubois, Menno Huisman, Felix van der Meer, Ankie Koopman (NOAC-VKA Working group); National Steering group on Integrated Anticoagulant Care

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Questions?

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