Monitoring oral anticoagulation
Philosophy and controversies

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*Paul, Paolo, Pablo….
Non-adherence is a problem

Size of problem

- Non-adherence of cardiovascular drug intake in USA is up to 50%
- 125,000 deaths in USA

Factors promoting adherence in medical practice

- Patients perceive symptom reduction
- Monitoring/feedback

“Despite the availability of effective treatment, over half of the patients being treated for hypertension drop out of care entirely within a year of diagnosis (15)…

… of those who remain under medical supervision only about 50% take at least 80% of their prescribed medications (16).

Consequently, because of poor adherence to antihypertensive treatment, approximately 75% of patients with a diagnosis of hypertension do not achieve optimum blood-pressure control (13,18).”
“Since cardiologists will not keep the majority of AF patients under regular surveillance, unless there are complicating factors, the patients […] on DOACs […] may lack proper surveillance with regard to side effects, complications, adherence etc.

This situation is disturbing given the fact that long term medication is prone not to be used properly by ± 50% of the patients!”

What happens when a patient taking a VKA with high INR variability is switched to an unmonitored oral anticoagulant that has:

- short half-life?
- 50% adherence?

Switched to NOAC:

Risk of bleeding may be reduced but is there any benefit?

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Drug monitoring; when is it useful?

Answer: When there is a dose response relationship with a relatively narrow therapeutic window between efficacy and harm, monitoring is useful:

- Factor VIII during surgery
- Insulin
- Gentamicin
- Vitamin K antagonists
- Why not direct oral anticoagulants?
... we don’t monitor DOACs

- DOACs are approved in certain doses, not to be titrated
- Pharmaceutical companies contend monitoring is not needed
  - Why?

- Does this withstand scrutiny?
Anticoagulant monitoring

**Useful: Tailored dose**

- Dose response effect important
  - LMWH
  - VKA
  - DOACs?

**Not useful: Fixed dose**

- Food and drug interactions
  - VKA
  - DOACs?
Aim of measuring VKA

**Therapeutic effect levels**
- Tailoring of dose to achieve ideal risk/benefit
- Emergencies
  - TE or bleeding
  - Safe levels pre-operatively
  - Overdose
  - Confirm effective reversal

**Assure adherence/compliance**
- Monitoring improves adherence
  - Adherence may be up to 80% with VKA
  - What is adherence with DOACs?
Aim of measuring DOACs

**Therapeutic levels**
- Tailoring vs fixed doses
  - Difficult
- Emergencies
  - TE or bleeding
  - Safe levels pre-operatively
  - Effective reversal
  - Overdose?
- Elderly?
- Comorbidities?
  - Impaired renal function; monitor creatinine x 2-3 annually
  - Impaired liver function

**Adherence/compliance**
- Unmonitored: 50%?

All the same reasons to monitor exist as with warfarin/VKA!
What to monitor?
## Monitoring antithrombotics; What to monitor?

<table>
<thead>
<tr>
<th><strong>Drug concentration</strong></th>
<th><strong>Biological effect</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotics</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>All or none effect</td>
</tr>
<tr>
<td></td>
<td>Antithrombotics; <strong>arguable</strong></td>
</tr>
<tr>
<td></td>
<td>- Platelet aggregation and release</td>
</tr>
<tr>
<td></td>
<td>- Multiplate®</td>
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<tr>
<td>Anticoagulants</td>
<td></td>
</tr>
<tr>
<td>VKA</td>
<td>Dose-response effect; <strong>useful</strong></td>
</tr>
<tr>
<td>no</td>
<td>- Anticoagulants</td>
</tr>
<tr>
<td>DOACs?</td>
<td>- Warfarin</td>
</tr>
<tr>
<td>possibly</td>
<td>- INR</td>
</tr>
<tr>
<td></td>
<td>- DTI</td>
</tr>
<tr>
<td></td>
<td>- Ecarin clotting time</td>
</tr>
<tr>
<td></td>
<td>- Hemoclot dTT</td>
</tr>
<tr>
<td></td>
<td>- aXA agents</td>
</tr>
<tr>
<td>Renal function</td>
<td>- Chromogenic anti-Xa assays</td>
</tr>
</tbody>
</table>
Is there a dose-response effect?

VKA

DOACs

Therapeutic Window

Source: ACC/AHA/ESC 2006 Practice Guidelines for the Management of Patients with Atrial Fibrillation
What to monitor (2)

Vitamin K antagonists
VKA concentration cannot be used

- A surrogate for biological effect is used;
  - prothrombin time (PT-INR)
Influence of VKD factors on the PT

Gudmundsdottir BR, Francis CW, Bjornsdottir A, Nellbring M, Onundarson PT. *Thromb Res* 2012;130:674-81
VKA biological effect is not correctly reflected by PT-INR
The INR needs Fiix-ing

Thrombin generation in relation to vitamin K factor deficiency

The sensitivity of the INR to FVII causes instability of anticoagulation

Fiix-trial: Total thromboembolism reduced with Fiix-INR monitoring (Stroke + SE + MI + TIA + VTE)

Intention to monitor analysis

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>d1-720</td>
<td>2.3% ppy</td>
</tr>
<tr>
<td>d181-720</td>
<td>2.2%</td>
</tr>
<tr>
<td>d1-720</td>
<td>1.2%</td>
</tr>
<tr>
<td>d181-720</td>
<td>1.1%*</td>
</tr>
</tbody>
</table>

Onundarson PT et al
www.thelancet.com/haematology
Published online May 26, 2015
http://dx.doi.org/10.1016/S2352-3026(15)00073-3
What to monitor (3)

DOACs
DOAC levels in relation to TE or MB

Are the tested doses in trials the best doses?

- We don’t know but they are the only approved doses!
- Tailored doses are not approved (like with VKA)

Concentrations in relation to untoward events

- Available for dabigatran etixilate (RE-LY) and edoxaban (ENGAGE trial)
- Not available for rivaroxaban or apixaban
From: The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)


Figure Legend:

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 indicate median dabigatran concentrations in the RE-LY trial with 10th and 90th percentiles. Conc. = concentration; DE = dabigatran etexilate; SEE = systemic embolic event(s).
Edoxaban Exhibits Concentration Dependent Relationships for **Ischemic Stroke** & **Life Threatening/Fatal Bleeds**

**Worse efficacy outcome than warfarin in AF**

Analysis shown for “typical” patient population: Age: 72 years old, Renal Function: (70.4 mL/min), 28.3% with prior stroke, 29.2% with baseline aspirin use.
Concentrations of DOAC and biological effect may be interchangeable.
What to monitor (4)

Single assay for all OACs?
Calibrated or not
Dilute PT or dilute Fiix-PT to measure all oral anticoagulants, UFH and enoxaparin

Increasing thromboplastin dilutions make the PT sensitive

Patient samples

Loic R. Letertre*, Brynja R. Gudmundsdottir*, Charles W. Francis†, Robert C. Goseling‡, Mika Skepholmi§, Rickard Malmstrom¶, Stephan Moll**, Emily Hawes**,††, Suzanne Francart††, and Pall T. Onundarson*‡‡

A single test to assay warfarin, dabigatran, rivaroxaban, apixaban, unfractionated heparin and enoxaparin in plasma. JTH 2016
Conclusions:
Should all oral anticoagulants be monitored?

You bet!

Could improve outcome through individualization of dose
Could improve adherence
Financial/nonfinancial disclosures: The authors have reported to CHEST the following: In the last 3 years:

- E. A. A. was an author on a number of systematic reviews on anticoagulation in patients with cancer.
- H. B. has received compensation for participation on advisory committees with speaking engagements sponsored by Sanofi-Aventis, Bayer Healthcare, and Daiichi-Sankyo. His institution has received grant funding (no salary support) from Daiichi-Sankyo for studying VTE treatment. He has also served as a coauthor of original studies using rivaroxaban (EINSTEIN, EINSTEIN Pulmonary Embolism[PE]) and edoxaban (Hokusai-VTE study).
- M. H. has received grant funding and has delivered talks related to long-term and extended anticoagulation and treatment of subsegmental PE. He has also authored several papers related to long-term and extended anticoagulation, treatment of subsegmental PE, and compression stocking in preventing postthrombotic syndrome.
- D. J. ’s institution has received grant funding (no salary support) from Instituto de salud Carlos III, Sociedad Española de Neumología y Cirugía Torácica, and NeumoMadrid for studying PE. He was a member of Steering Committee of the Pulmonary Embolism Thrombosis Study (PEITHO), a principal investigator of an original study related to the role of the inferior vena cava filter in addition to anticoagulation in patients with acute DVT or PE and has participated in the derivation of scores for identification of low-risk PE. He has delivered talks related to treatment of acute PE.
- C. K. has been compensated for speaking engagements sponsored by Boehringer Ingelheim and Bayer Healthcare related to VTE therapy. His institution has received grant funding (no salary support) from the National Institutes of Health related to the topic of catheter-assisted thrombus removal in patients with leg DVT. He has also published many studies related to long-term anticoagulation and compression stockings in preventing postthrombotic syndrome.
- L. M. has frequently lectured on the duration of long-term anticoagulation and is a coauthor on several risk-stratification papers. She has received honoraria from CHEST Enterprises for VTE talks.
- T. M. and C. S. K. have received honoraria from Chest Enterprises for VTE Prep Courses. T. M.’s institution has received grant funding (no salary support) from Portola Pharmaceuticals for the Acute Medically Ill VTE Prevention With Extended Duration Betrixaban Study (APEX) related to extended prophylaxis against VTE with betrixaban. T. M.’s institution received grant support from Bayer Pharmaceuticals for a research project concerning the etiology of chronic thromboembolic pulmonary hypertension. He has also authored textbook chapters related to thrombolytic interventions in patients with acute PE and pulmonary thromboendarterectomy in chronic thromboembolic pulmonary hypertension. S. M. S.’s and S. C. W.’s institution has received grant funding (no salary support) from the Canadian Institutes of Health for the D-dimer Optimal Duration Study Phase II (DODSExtension), from Washington University via the National Institutes of Health (Genetic Informatics Trial), Bayer related to VTE (EINSTEIN studies), and from Bristol-Myers Squibb related to apixaban for the Secondary Prevention of Thromboembolism (Apixaban for the Secondary prevention of Thromboembolism: A prospective Randomized Outcome pilot study among patients with the Antiphospholipid Syndrome).
- J. R. E. V.’s institution has received grant funding (no salary support) from Bristol-Myers Squibb for evaluating the role of apixaban for long-term treatment of VTE.
- P. W. is a coinvestigator on a grant regarding the treatment of subsegmental PE. He has authored several studies and grants related to the long-term and extended anticoagulation (using vitamin K antagonists and the direct oral anticoagulants).
- P. W. has received grant funding from Bristol-Myers Squibb and has received honoraria for talks from Bayer. E. A. A., H. B., C. K., P. W., and S. C. W. participated in the last edition of the CHEST Antithrombotic Therapy for VTE Disease Guidelines (AT9).
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