Modern concept of NOACs – opportunities and challenges

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Opportunities

- predictable dose response
- fixed dosing
- consistently improved efficacy and toxicity profile in various subpopulations (age, weight, comorbidities)
- no or minimal food / drug interactions
- dose modification possible if needed
Current challenges

• anticoagulation – the mere size of the problem

• finding the right drug for the indication

• to prevent side effects

• how to deal with bleeding
Frequency of atrial fibrillation

Go et al. JAMA 2001

Women (n=7795)
Men (n=10179)

Prevalence (%)
Current challenges

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• to prevent side effects
• how to deal with bleeding
Indications NOACs

**Dabigatran**
- direct F. IIa-Inhibitor, twice daily
- EMA
  - Orthopaedics 4/2008
  - SPAF 8/2011
- Swissmedic
  - SPAF 5/2012
- FDA
  - SPAF 10/2010

**Rivaroxaban**
- direct F. Xa Inhibitor, once daily
- EMA
  - Orthopaedics 7/2008
  - SPAF 2/2012
  - DVT treatment, prophylaxis 2/2012
- Swissmedic
  - Orthopaedics 12/2008
  - SPAF 4/2012
  - DVT treatment, DVT/PE prophylaxis 4/2012
- FDA
  - Orthopaedics 6/2011
  - SPAF 11/2011
  - DVT/PE treatment, prophylaxis 11/2012

**Apixaban**
- direct F. Xa Inhibitor, twice daily
- EMA
  - Orthopaedics 5/2011
  - SPAF 11/2012
- Swissmedic
  - Orthopaedics 8/2011

**Edoxaban**
- direct F. Xa Inhibitor, once daily
- JMA
  - Orthopaedics 7/2011
Boehringer Ingelheim discontinues Phase II trial in patients with artificial heart valves

For Non-US, Non-UK & Non-Canadian Media Only

Ingelheim, Germany, 11 December 2012 – Boehringer Ingelheim has taken the voluntary decision to discontinue treatment with the oral anticoagulant dabigatran etexilate in a phase II clinical trial in patients with artificial heart valves. The company based its decision on interim results from the phase II RE-ALIGN study, which showed that treatment with dabigatran etexilate is associated with increased risks of intracranial hemorrhage and other bleeding complications as compared to standard therapy with warfarin.

APPRAISE-2: Apixaban risks outweigh benefits in high-risk ACS

July 24, 2011 – Reed Miller

Kyoto, Japan - The full results of the APPRAISE-2 trial of the anticoagulant apixaban (Eliquis, Bristol-Myers Squibb/Pfizer) in high-risk acute coronary syndrome (ACS) patients, which was stopped prematurely in November 2010, are now published online in the New England Journal of Medicine [1]. Lead investigator Dr John Alexander (University of Rochester Medical Center) found that both the risk of major bleeding and death from any cause was significantly lower in patients treated with apixaban compared to placebo.

FDA refuses ACS indication for rivaroxaban—for now

ACUTE CORONARY SYNDROMES

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Age, polymorbidity and medications

• Medical School Hannover, Germany, 2007: GP setting review on polymedication in elderly patients

• 25% of all patients > 70 years are on 5+ medications
• mean: 3.7 prescribed medications and 1.4 OTC medications

• GP knows about all medications taken in 43% of cases
• relevant interactions / contraindications in 20-25%
• 3-6% of all hospitalisations due to direct medication influence

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<thead>
<tr>
<th><strong>β-Lactam antibiotics</strong></th>
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<td>Penicillins</td>
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<td>Carbenicillin, 49-52 mezlocillin, 53,54 piperacillin, 54,55 ticarcillin 54,56</td>
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<td>Apalillin, 57 methicillin 58</td>
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<td>Ampicillin, 58 penicillin G 58,59</td>
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<td>Nafcillin 62</td>
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<td>Cephalosporins</td>
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<td>Cephalothin 63</td>
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<td>Cefoperazone 61</td>
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<td>Cefotaxime 54</td>
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<td>Moxalactam 61,64</td>
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<td>Nifedipine, 73 nitroglycerin 74,75</td>
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<td>Quinidine 76</td>
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<td>Abnormal platelet aggregation</td>
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<td>Chlorpromazine 41</td>
<td>Abnormal platelet aggregation in vitro</td>
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<td>Benoxinate, 82 benzocaine, 81 butacaine, 81,83 cocaine, 82 cyclaine, 83 dibucaine, 81 hydroxychloroquine, 83 lidocaine, 83 piperocaine, 83 proparacaine, 82 procaine, 81,83 tetracaine 81,83</td>
<td>Abnormal platelet aggregation in vitro</td>
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<td>Halothane, 84 heroin 85</td>
<td>Abnormal platelet aggregation and bleeding time</td>
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<td>Abnormal platelet aggregation</td>
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<td>Dextran, 106,109 epoprostenol, 108 nitrofurantoin 102</td>
<td>Abnormal platelet aggregation and bleeding time</td>
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<td>Iloprost 103</td>
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<td>Ticlopidine 104,105</td>
<td>Abnormal platelet aggregation and bleeding time; clinical bleeding</td>
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<td>Ginger, 106,107 onion, 108 vitamin C, 108 vitamin E 110</td>
<td>Abnormal platelet aggregation</td>
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<td>Cumin, 111 turmeric, 112 cloves 107</td>
<td>Abnormal platelet aggregation in vitro</td>
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<td>Alcohol, 112,113 n-3 fatty acids 114,115</td>
<td>Abnormal platelet aggregation and bleeding time</td>
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<tr>
<td>Chinese black tea fungus (tzo-er), 116 garlic 108,117</td>
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Challenges to come

- treatment frequency using NOACs will increase (A.fib.)
- patients using NOACs have frequent co-medications due to co-morbidity
- co-medication frequently (!) with platelet-inhibiting properties

→ in case of bleeding:
  all potential pathophysiology to be considered
Swiss recommendations for the perioperative use of NOACs
Perioperative use of NOACs – planned intervention

- consider: renal function, hepatic function, potential interactions
Current challenges

• anticoagulation – the mere size of the problem
• finding the right drug for the indication
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• how to deal with bleeding
PK/PD of single-dose edoxaban

- Rapidly absorbed with Cmax within 1-2 hours
- Cmax and AUC increased in a dose-related manner
- Rapid increase in PT with peak effect within 1-2 hours

Cmax, maximum observed plasma concentration; AUC, area under the curve; PT, prothrombin time

Summary

- against expectations from in vitro studies, early clinical experience reveals no clear cut clinical improvement with procoagulants in case of bleeding under NOACs

- hemodialysis in case of Dabigatran accumulation seems beneficial
Conclusions - opportunities and challenges of NOACs

• opportunities:
  – higher efficacy
  – lower bleeding rates
  – predictable pharmacokinetics with short half life
  – periinterventional on /off use

• challenges:
  – number of patients to be anticoagulated
  – not for all indications
  – co-medications
  – bleeding management
Thank you for your attention.

www.zlmsg.ch  wolfgang.korte@zlmsg.ch
Pharmakokinetik Apixaban

Pharmakokinetik Rivaroxaban und Dabigatran


- Rivaroxaban:
  - Elderly females: n=6
  - Elderly males: n=6

- Dabigatran:
  - Plasma-Konzentration in ng/mL
  - Time (h)

Die Grafik unten zeigt die Dabigatran-Konzentrationen in ng/mL über die Zeit in Stunden. Die Konzentrationen von INR und aPTT, ECT sind ebenfalls auf der Grafik als Verhältnis eingezeichnet.
Perioperative NOACs – epidurals

10 mg Rivaroxaban
Letzte Rivaroxaban-Dosierung Katheter setzen oder ziehen* Nächste Rivaroxaban-Dosierung
18 h warten 6 h warten

20 l 15 mg Rivaroxaban
Letzte Rivaroxaban-Dosierung Katheter setzen oder ziehen* Nächste Rivaroxaban-Dosierung
>24 h warten 6 h warten

*Nach traumatischer Punktion sollte die Verabreichung von Rivaroxaban für 24 Stunden aufgeschoben werden

OP-Ende Epidural/intrathekal Verweilkatheter ziehen 12–24 h 5 h 12 h 12 h