Modern concept of NOACs – opportunities and challenges

Prof. Wolfgang Korte

Center for Laboratory Medicine,
Clinical Chemistry and Haematology

St. Gallen, Switzerland

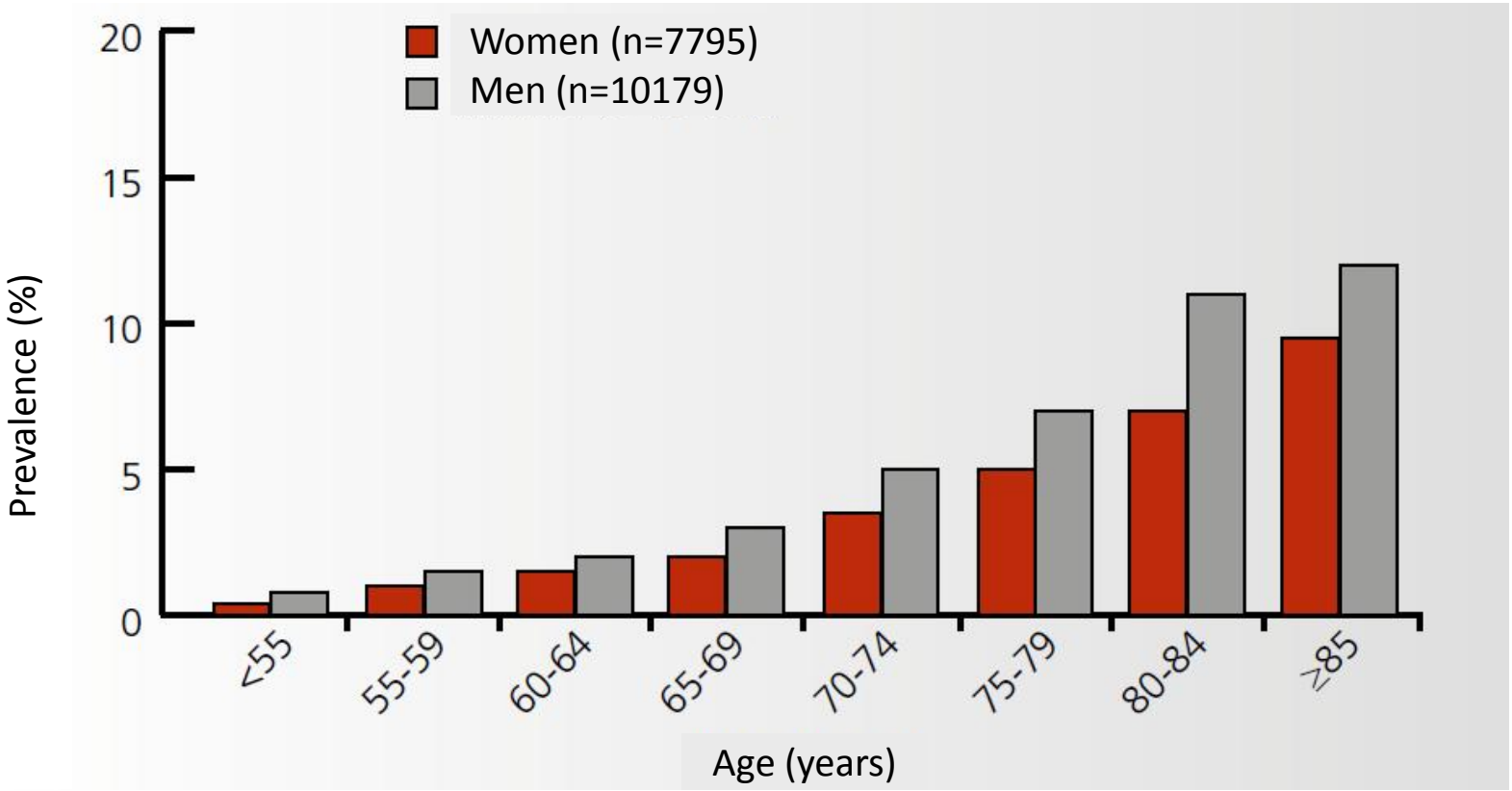
Opportunities

- 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

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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

11 December 2012

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
results in t

heartwire

ACUTE CORONARY SYNDROMES

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

JULY 24, 2011 Reed Miller

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1 Comments Read later Print Font size A A A Cite

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**

heartwire

ACUTE CORONARY SYNDROMES

FDA refuses ACS indication for rivaroxaban—for now

Current challenges

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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

http://www.uniklinikum-saarland.de/fileadmin/UKS/Lehre/Studiengaenge/Humanmedizin/2.Studienabschnitt/Allgemeinmedizin/Downloads/WS1112/Mulitmorb_und_Polypharma.pdf

Table 1. Drugs, Foods, Spices, and Vitamins That May Cause Abnormalities of Platelet Function.*

β-Lactam antibiotics	
Penicillins	
Carbenicillin,[49-52] mezlocillin,[53,54] piperacillin,[54,55] ticarcillin[54,56]	Abnormal platelet aggregation and bleeding time; clinical bleeding
Apalcillin,[57] methicillin[58]	Abnormal platelet aggregation
Ampicillin,[58] penicillin G[58,59]	Abnormal platelet aggregation and bleeding time
Sulbenicillin[60]	Abnormal platelet aggregation in vitro
Azlocillin[61]	Abnormal bleeding time
Nafcillin[62]	Abnormal bleeding time; clinical bleeding
Cephalosporins	
Cephalothin[63]	Abnormal platelet aggregation
Cefoperazone[51]	Abnormal bleeding time
Cefotaxime[54]	Abnormal bleeding time; clinical bleeding
Moxalactam[51,64]	Abnormal platelet aggregation and bleeding time; clinical bleeding
Cardiovascular drugs	
Dipyridamole[65]‡	—
Diltiazem,[66]isosorbide dinitrate,[67] isosorbide mononitrate,[68] nimodipine,[69] propranolol,[70] sodium nitroprusside,[71] verapamil[72]	Abnormal platelet aggregation
Nifedipine,[73] nitroglycerin[74,75]	Abnormal platelet aggregation and bleeding time
Quinidine[76]	Abnormal bleeding time; clinical bleeding
promazine,[81] trifluoperazine	
Chlorpromazine[41]	Abnormal platelet aggregation
Psychotropic drugs	
Amitriptyline,[80] fluphenazine,[81] haloperidol,[81] imipramine,[80] nortriptyline,[80] promazine,[81] trifluoperazine[81]	Abnormal platelet aggregation in vitro
Chlorpromazine[41]	Abnormal platelet aggregation
Anesthetics and narcotics	
Benoxinate,[82] benzocaine,[81] butacaine,[81,83] cocaine,[83] cyclaine,[83] dibucaine,[81] hydroxychloroquine,[83] lidocaine,[83] piperocaine,[83] proparacaine,[82] procaine,[81,83] tetracaine[81,83]	Abnormal platelet aggregation in vitro
Halothane,[84] heroin[85]	Abnormal platelet aggregation and bleeding time
Clofibrate,[97] guaifenesin,[41] ketanserin[98]	Abnormal platelet aggregation
Dextran,[99,100] epoprostenol,[101] nitrofurantoin[102]	Abnormal platelet aggregation and bleeding time
Iloprost[103]	Abnormal platelet aggregation in vitro
Ticlopidine[104,105]	Abnormal platelet aggregation and bleeding time; clinical bleeding
Foods, spices, and vitamins	
Ginger,[106,107] onion,[108] vitamin C,[109] vitamin E[110]	Abnormal platelet aggregation
Cumin,[111] turmeric,[111] cloves[107]	Abnormal platelet aggregation in vitro
Alcohol,[112,113] n−3 fatty acids[114,115]	Abnormal platelet aggregation and bleeding time
Chinese black tree fungus (mo-er),[116] garlic[108,117]	Abnormal platelet aggregation; clinical bleeding

George et al., NEJM, 1991;324:27

Challenges to come

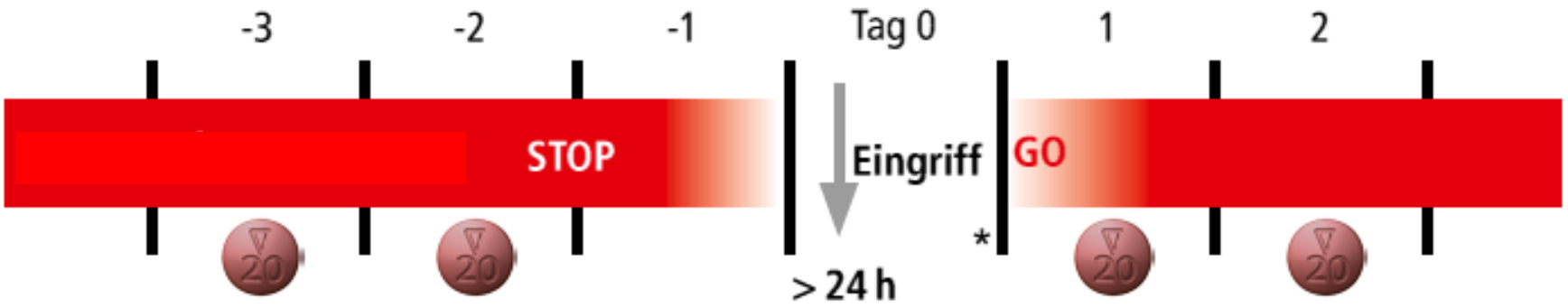
- treament frequency using NOACs will increase (A.fib.)
- patients using NOACs have frequent co-medications due to co-morbidity

- co-medication frequently (!) with platelet-inhibiting properties

→ in case of bleeding:
all potential pathophysiologies 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

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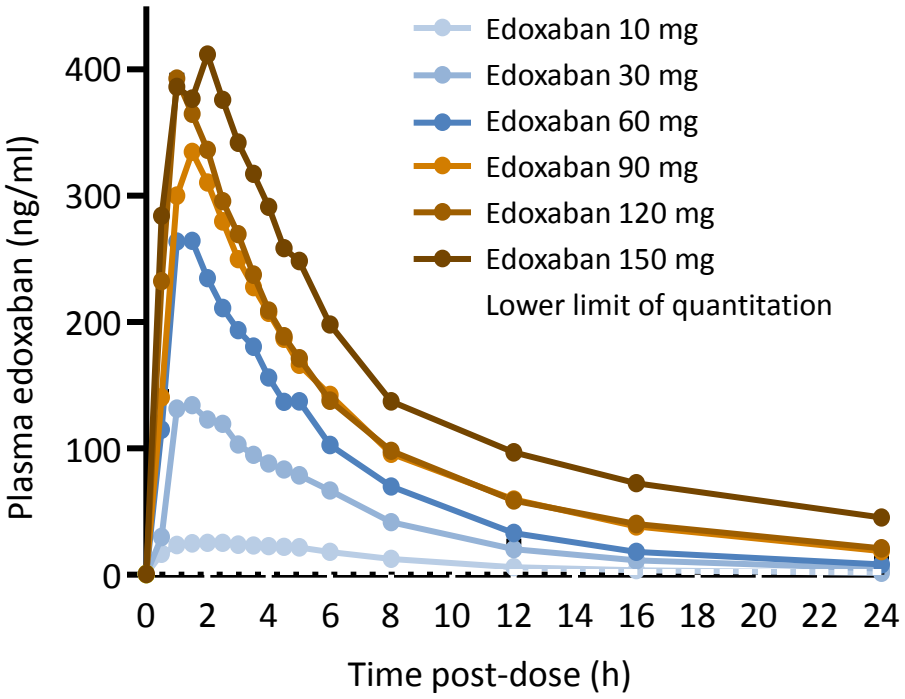
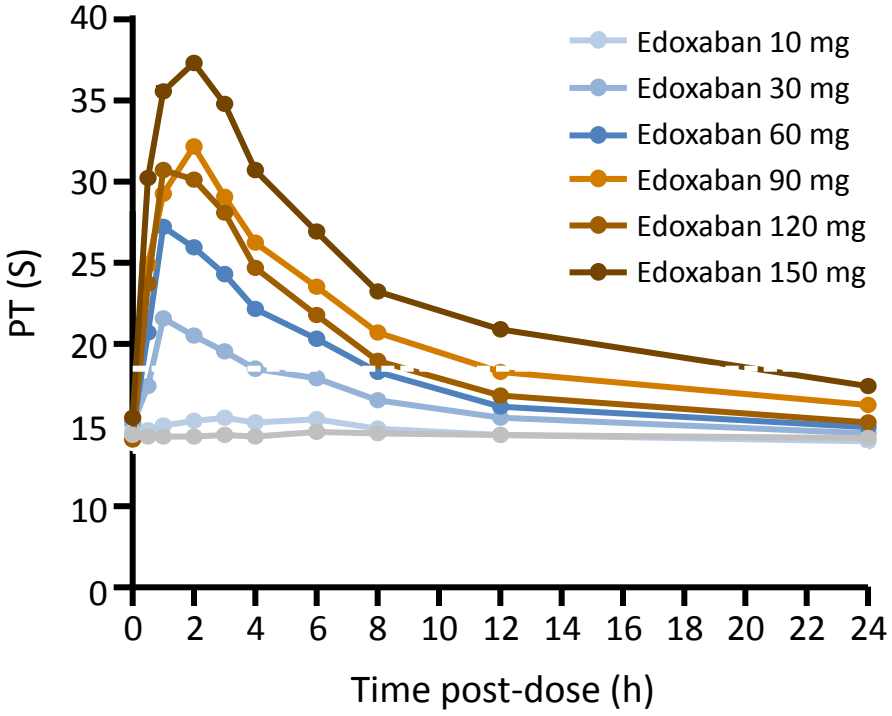
PK/PD of single-dose edoxaban





- 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

Dotted lines represent the reference range for the analysis

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

Ogata et al. J Clin Pharmacol 2010;50:743-753

Life-threatening bleeding in four patients with an unusual excessive response to dabigatran: Implications for emergency surgery and resuscitation

doi:10.1160/TH12-03-0149
Thromb Haemost 2012; 108: 583–585

Treatment of Dabigatran-Associated Bleeding: Case Report and Review of the Literature

Journal of Pharmacy Practice
00(0) 1-6

DOI: 10.1177/0897190012465955
http://jpp.sagepub.com
SAGE

Lisa M. Harinstein, PharmD, BCPS[1], Joseph W. Morgan, MD[2], and Nicholas Russo, MD[2]

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

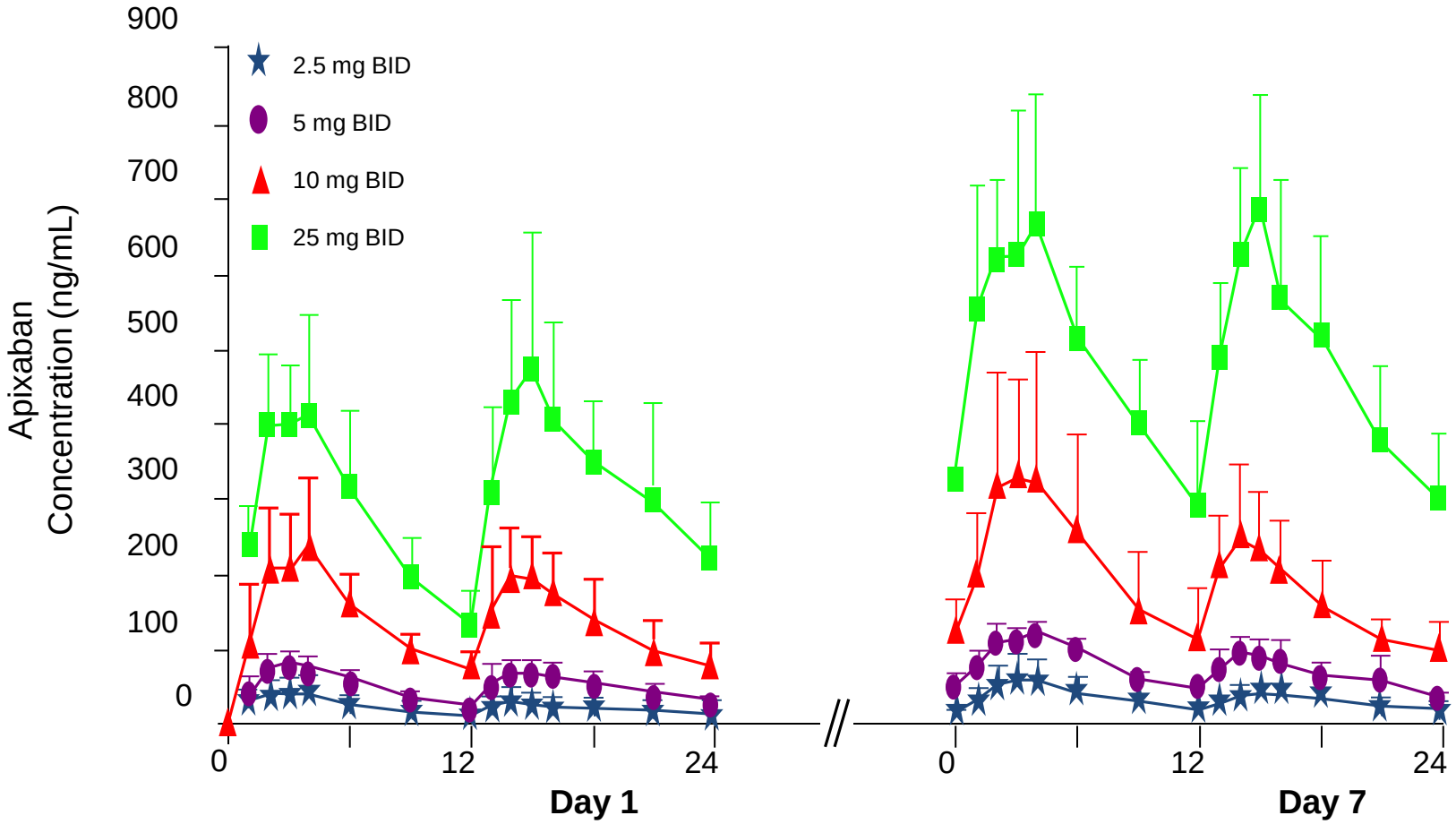
- challenges:
  - number of patients to be anticoagulated
  - not for all indications
  - co-medications
  - bleeding management

Thank you for your attention.

www.zlmsg.ch

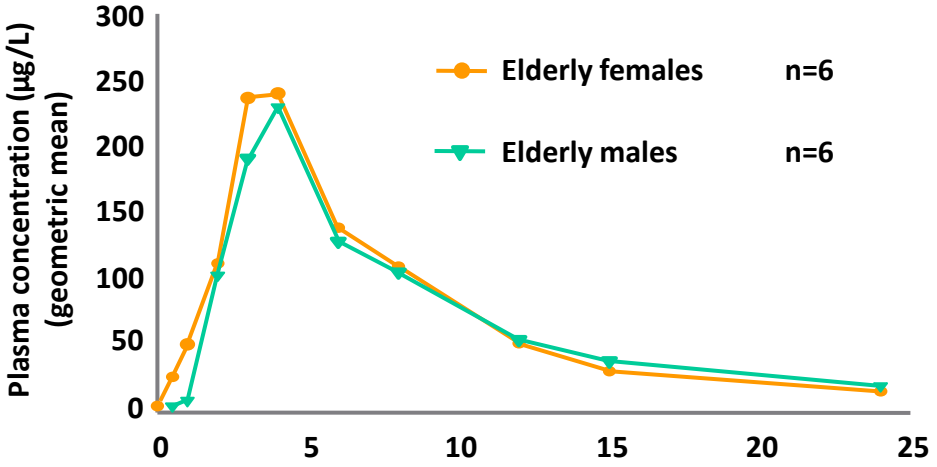
wolfgang.korte@zlmsg.ch

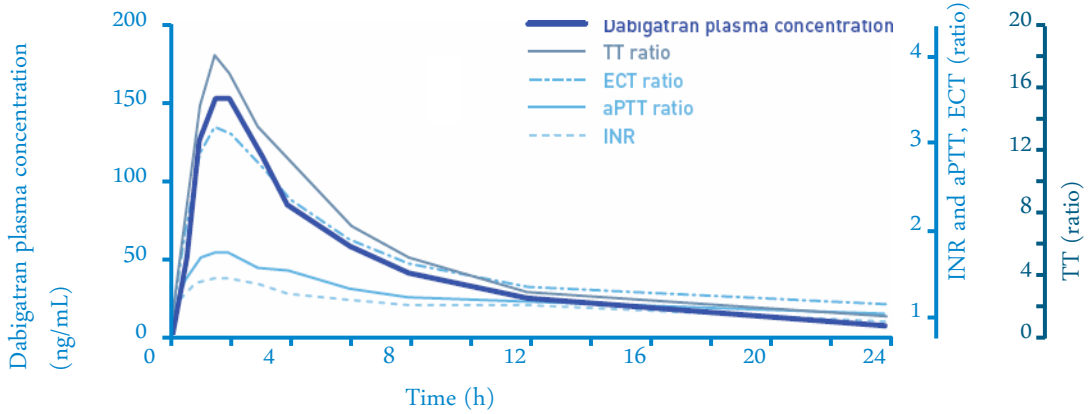
Pharmakokinetik Apixaban



Frost C et al., ISTH; July 2007; Geneva, Switzerland. Poster P-M-664.

Pharmakokinetik Rivaroxaban und Dabigatran





Perioperative NOACs – epidurals