The New Anticoagulants
and the Future of Anticoagulation

Raffaele De Caterina

“G. d’Annunzio” University – Chieti and
“G. Monasterio” Foundation – Pisa, Italy

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Prof. Raffaele De Caterina

Disclosures

- Co-author of 2010-2012 ESC Guidelines on Atrial Fibrillation
- Steering Committee member, National Coordinator for Italy, and Co-author of ACTIVE, APPRAISE-2, ARISTOTLE, AVERROES
- Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo
Anticoagulants in Medicine

- For acute/short term use (parenteral)
  - Unfractionated heparin
  - Low molecular weight heparin - LMWH
  - Fondaparinux-Idrabiotaparinux
  - Bivalirudin

- Anticoagulants for long-term use (oral)
  - Vitamin K antagonists (VKA)
  - Direct oral anticoagulants (DOA)
prothrombin (II) → thrombin (IIa) → free vWF → prothrombin (II) → fibrinogen (I) → THROMBIN (IIa) → fibrinogen (I) → FIBRIN

TF/VIIa

Initiation

Amplification-Propagation

VIIIa

X

IX

IXa

Thrombin activity

II

IIa

Fibrinogen

Fibrin

Vitamin K₂ (menaquinone)

coumarin 4-hydroxy-coumarin  warfarin  Indane-1,3-dione

phenoprocoumon  acenocoumarol  phenindione  fluindione
Oral anticoagulants: VKA

- **Dosing**
  - Oral; varies, depending on coagulation monitoring tests

- **Monitoring**
  - Usually monthly, testing INR
  - INR target of 2.5, range 2.0–3.0

- **Adverse events**
  - Bleeding, bruising
  - Many significant and potential food and drug interactions

- **Unique advantage**
  - Only anticoagulant available for long-term use

Harvey & Champe. Pharmacology 1997
The discovery of warfarin

- The sweet clover problem
- Link’s isolation of the oral anticoagulant
- From test tube to rat poison – Karl Link
- From rat poison to clinical application
1951 advertisement for warfarin
Warfarin for stroke prevention in AF*

- AFASAK I (n=1,007)
- AFASAK II (n=677)
- EAFT (n=1,007)
- PATAF (n=729)
- SPAF II (n=1,100)
- All trials (n=3,420)

- n=2,837
- 205 strokes
- RRR 36% (95% CI: 14%–52%) for all stroke
- RRR 46% (27%–60%) for ischaemic stroke

*Valvular and non-valvular; RRR, relative risk reduction

AF: ACTIVE-W trial

No benefit from adding clopidogrel to ASA vs VKA

Cumulative risk of primary outcome

Risk reduction = 1.44 (1.18–1.76), \( p=0.0003 \)

- Stopped early
- Efficacy
  - VKA: 165 (3.93%/year)
  - Clopidogrel/ASA: 234 (5.5%/year)
- Safety
  - No significant difference in major haemorrhage rates
    - VKA: 2.2%
    - Clopidogrel/ASA: 2.4%

Active Writing Group. Lancet 2006; Hohnloser. US Cardiovascular Disease 2007
... and they have allowed

- the long-term prevention/treatment of venous thromboembolism (deep vein thrombosis/pulmonary embolism)
- the development of
  - mechanical valves
  - the artificial heart
  - the ventricular assist devices
  ...
Warfarin: contraindications

- Pregnancy
  - Associated with developmental abnormalities
- Threatened abortion, eclampsia and pre-eclampsia
- Recent surgery
  - CNS; eye; traumatic surgery, resulting in large open surfaces
- Bleeding tendencies associated with active ulceration or overt bleeding
  - GI, GU or RT
  - Cerebrovascular haemorrhage aneurysms—cerebral, dissecting aorta
  - Pericarditis and pericardial effusions
  - Bacterial endocarditis
- Unsupervised patients with
  - Senility
  - Alcoholism
  - Psychosis, or
  - Other lack of patient co-operation
- Spinal puncture
- Any diagnostic or therapeutic procedures with potential for uncontrollable bleeding
- Miscellaneous
  - Major regional
  - Lumbar block anaesthesia
  - Malignant hypertension
  - Known warfarin hypersensitivity

CNS, central nervous system; GI, gastrointestinal; GU, genitourinary; RT, reproductive tract
www.rxlist.com/cgi/generic/warfarin_ad.htm
Warfarin: drug interactions

Many drugs have the potential to interact with warfarin

- Atorvastatin, simvastatin
- Esomeprazole, lansoprazole
- Paracetamol, ASA, ibuprofen
- Propranolol, naproxen
- Chloramphenicol, clarithromycin, tetracycline, penicillin G, metronidazole...
- Alcohol

Specific drugs reported
- acetaminophen
- alcohol
- allopurinol
- aminosalicylic acid
- amiodarone HCI
- amoxicillin
- atorvastatin
- azathioprine
- bivalirudin
- capecitabine
- cefamandole
- cefazolin
- cefoperazone
- cefotetan
- cefoxitin
- ceftriaxone
- celecoxib
- cerivastatin
- ciprofloxacin
- clindamycin
- clarithromycin
- clofibrate
- COUMADIN overdose
- cyclophosphamide
- danazol
- dextran
- dexdolloxylamine
- diazoxide
- diclofenac
- dicumarol
- diflunisal
- disulfiram
- doxycycline
- edrophonium
- esomeprazole
- ethacrynic acid
- ezetimibe
- famotidine
- fenoprofen
- fluconazole
- fluorouracil
- fluoxetine
- flutamide
- fluvalastin
- fluvoxamine
- gefitinib
- gemfibrozil
- glucagon
- halothane
- ibuprofen
- indomethacin
- influenza virus vaccine
- itraconazole
- ketoprofen
- knocksap
- lansoprazole
- levamisole
- levofloxacin
- levotyroxine
- lidocaine
- lovastatin
- mefenamic acid
- methimazole
- methylprednisolone
- methylphenidate
- methylsulfonyl fluoride
- nicardipine
- nimodipine
- nimodipine (intravaginal, oral, systemic)
- norfloxacin
- omeprazole
- oxaprozin
- oxalaparizone
- oxazepam
- oxymetholone
- pantoprazole
- penicillin G, intravenous
- phenytoin
- phenylbutazone
- phenytoin
- Piperacillin
- pravastatin
- prednisone
- propafenone
- propamidine isethionate
- propylthiouracil
- quinidine
- quinolones
- quinidoxamine
- ranitidine
- rofecoxib
- simvastatin
- streptokinase
- streptokinase
- sulfa methoxazole
- sulfamethoxazole
- sulfinpyrazone
- sulfonamides
- tamoxifen
- ticarcillin
- ticlopidine
- tissue plasminogen activator (t-PA)
- tolbutamide
- tramadol
- trimethoprim/sulfamethoxazole
- uricase
- valdecoxib
- valproate
- vitamin E
- zafirlukast
- zileuton

www.rxlist.com/cgi/generic/warfarin_ad.htm
VKA: perhaps the main problem...

- The need for monitoring
Underutilization of anticoagulation in AF*

Approximately half of high-risk patients with AF receive warfarin therapy

13 community hospitals

- 53% warfarin therapy
- 47% No warfarin therapy

21 academic hospitals

- 53% warfarin therapy
- 47% No warfarin therapy

*US population January–December 2002
Waldo et al. J Am Coll Cardiol 2005
Therefore...

- a strong need for safe, effective, oral anticoagulants that do not require monitoring!!!
THROMBIN
and
ODTI

Direct
THROMBIN and ODTI Reversible
Inhibition of fibrin bound thrombin
Inhibition of free and fibrin-bound thrombin

\[ IC_{50} = 92 \text{ nmol/L} \]

\[ IC_{50} = 89 \text{ nmol/L} \]
Primary analyses
Intention-to-treat analysis

ximelagatran better

SPORTIF III
p = 0.10

SPORTIF V
p = 0.13

Pooled
p = 0.94

warfarin better

Difference in absolute event rates (ximelagatran - warfarin)

-0.66
p = 0.10

+0.45
p = 0.13

-0.03
p = 0.94

Presented at AHA 2003
ALAT > 3x ULN

Incidence (%)

8
7
6
5
4
3
2
1
0

SPORTIF III

SPORTIF V

Pooled

warfarin
ximelagatran

0.8%
0.8%
0.8%

6.3%
6.0%
6.1%

Presented at AHA 2003
A New Era in Anticoagulation

Initiation

TF/VIIa

Amplification-Propagation

VIIIa

IXa

X

IX

Va

Xa II

Fibrinogen

Fibrin

Thrombin activity

Direct dabigatran

Direct

rivaroxaban
apixaban
edoxaban

Anticoagulants – a classification

Anticoagulants

Parenteral

Indirect

Thrombin inhibitors

UFH
LMWH
fondaparinux
M118

Indirect

hirudin
bivalirudin
argatroban

Direct

Factor Xa inhibitors

oralixaban

Direct

VKA

dabigatran

Oral

Indirect

Factor Xa inhibitors

rivaroxaban

Direct

Factor Xa inhibitors

apixaban

edoxaban

The phase III development of a new anticoagulant

- VTE prevention (usually in orthopedic surgery)
- VTE treatment (DVT and PE)
- Atrial fibrillation
- Acute coronary syndromes
A meta-analysis of NOACs in THR or TKR including all phase III trials

**VTE/all-cause death**

### Favours oral drug

- Dabigatran
  - RE-NOVATE
  - RE-MODEL
  - RE-MOBILIZE
  - RE-NOVATE II
  - Overall

### Favours enoxaparin

- 0.97 (0.82–1.13)
- 0.90 (0.63–1.29)
- 0.88 (0.63–1.22)
- 1.03 (0.93–1.15)

**RR = 1.03**

**p = 0.58**

### Favours oral drug

- Rivaroxaban
  - RECORD1
  - RECORD2
  - RECORD3
  - RECORD4
  - Overall

### Favours enoxaparin

- 0.30 (0.18–0.51)
- 0.21 (0.13–0.35)
- 0.51 (0.39–0.65)
- 0.69 (0.51–0.92)
- 0.46 (0.39–0.54)

**RR = 0.46**

**p < 0.001**

### Favours oral drug

- Apixaban
  - ADVANCE-1
  - ADVANCE-2
  - ADVANCE-3
  - Overall

### Favours enoxaparin

- 1.02 (0.78–1.32)
- 0.62 (0.51–0.74)
- 0.36 (0.23–0.56)
- 0.67 (0.58–0.77)

**RR = 0.67**

**p < 0.001**

**Major bleeding**

### Favours oral drug

- 1.14 (0.46–2.78)
- 0.42 (0.15–1.19)
- 1.29 (0.70–2.37)
- 1.54 (0.67–3.55)
- 1.09 (0.74–1.61)

### Favours enoxaparin

- 3.02 (0.61–14.95)
- 1.00 (0.06–15.98)
- 1.18 (0.40–3.52)
- 2.47 (0.78–7.86)
- 1.85 (0.94–3.63)

**RR = 1.09**

**p = 0.66**

### Favours oral drug

- 0.50 (0.24–1.02)
- 0.65 (0.28–1.49)
- 1.22 (0.65–2.26)
- 0.78 (0.52–1.16)

### Favours enoxaparin

- 1.22 (0.65–2.26)
- 0.78 (0.52–1.16)

**RR = 1.85**

**p = 0.07**

### Favours oral drug

- 0.36 (0.23–0.56)
- 0.67 (0.58–0.77)

### Favours enoxaparin

- 0.30 (0.18–0.51)
- 0.21 (0.13–0.35)

**RR = 0.30**

**p = 0.21**

ACCP 2012 Treatment of VTE

Phases of anticoagulation

- **Initial** (0 to ~7 days)
  - Parenteral*
    - Heparin, LMWH, fondaparinux

- **Long-term** (~7 days to ~3 months)
  - Vitamin K antagonist or other agent†
    - Includes LMWH, dabigatran, rivaroxaban

- **Extended** (~3 months to indefinite)
RE-LY®: one of the largest AF outcomes trials

**RE-LY®:**  
**R**andomized **E**valuation of **L**ong-term anticoagulant therapy

- 18,113 patients randomized during 2 years¹,²
- 50% of patients naïve to previous oral anticoagulant
- Median treatment duration: 2 years
- 951 centres in 44 countries
- December 2005 to March 2009
- Results first presented at ESC Congress 2009 and published online in the *New England Journal of Medicine* on 30 Aug 2009

ESC = European Society of Cardiology
RE-LY®: study design

Primary objective: to establish the non-inferiority of dabigatran to warfarin

Minimum 1-year follow-up, maximum of 3 years and median of 2 years of follow-up

*Severe heart-valve disorder, stroke ≤14 days or severe stroke ≤6 months before screening, increased haemorrhage risk, creatinine clearance <30 mL/min, active liver disease, pregnancy

BID = twice daily; INR = international normalized ratio; R = randomization

Time to first stroke or systemic embolism

**Warfarin**

- **RR 0.90**
  - (95% CI: 0.74–1.10)
  - P<0.001 (NI)
  - P=0.30 (Sup)

**Dabigatran 110 mg BID**

- **RR 0.65**
  - (95% CI: 0.52–0.81)
  - P<0.001 (NI)
  - P<0.001 (Sup)

**Dabigatran 150 mg BID**

**RRR** 35%

---

BID = twice daily; NI = non-inferiority; RR = relative risk; RRR = relative risk reduction; Sup = superiority

Incidence of stroke or systemic embolism

RR 0.90 (95% CI: 0.74–1.10)
P<0.001 (NI)

RR 0.65 (95% CI: 0.52–0.81)
P<0.001 (Sup)

RR 0.90
(95% CI: 0.74–1.10)
P<0.001 (NI)

RR 0.65
(95% CI: 0.52–0.81)
P<0.001 (Sup)

RRR 35%

Events/number:
Dabigatran 110 mg BID
183/6015

Dabigatran 150 mg BID
134/6076

Warfarin
202/6022

Dabigatran 110 mg BID
1.54

Dabigatran 150 mg BID
1.11

Warfarin
1.71

BlD = twice daily; NI = non-inferiority; RR = relative risk; RRR = relative risk reduction; Sup = superiority
Ischaemic stroke

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events/n</th>
<th>Ischaemic stroke (%)/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 mg BID</td>
<td>152/6015</td>
<td>1.28%</td>
</tr>
<tr>
<td>Dabigatran 150 mg BID</td>
<td>103/6076</td>
<td>0.86%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>134/6022</td>
<td>1.14%</td>
</tr>
</tbody>
</table>

- **HR 1.13** (95% CI: 0.89–1.42)  
  - RRR 25%  
  - P=0.31

- **HR 0.75** (95% CI: 0.58–0.97)  
  - RRR 25%  
  - P=0.03 (Sup)

BID = twice daily; hr = hazard ratio; RRR = relative risk reduction; Sup = superiority
Pradaxa®: EU SmPC 2012
Haemorrhagic stroke

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Rate (%), RR, 95% CI, P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 mg BID</td>
<td>6015</td>
<td>0.12%, RR 0.31 (0.17–0.56), P&lt;0.001 (Sup)</td>
</tr>
<tr>
<td>Dabigatran 150 mg BID</td>
<td>6076</td>
<td>0.10%, RR 0.26 (0.14–0.49), P&lt;0.001 (Sup)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>6022</td>
<td>0.38%, RR 0.31 (0.17–0.56), P&lt;0.001 (Sup)</td>
</tr>
</tbody>
</table>

BID = twice daily; RR = relative risk; RRR = relative risk reduction; Sup = superiority
AVERROES Design

36 countries, 522 centres

AF and ≥1 risk factor, and demonstrated or expected unsuitable for VKA

Apixaban 5 mg BID
2.5 mg BID in selected patients

5,600 patients

ASA (81-324 mg/d)

Primary Outcome: Stroke or Systemic Embolic Event (SEE)
Stroke or Systemic Embolic Event

RR = 0.46
95% CI = 0.33-0.64
p < 0.001

Cumulative Risk

No. at Risk
ASA 2791 2720 2541 2124 1541 626 329
Apix 2809 2761 2567 2127 1523 617 353

Months
0 3 6 9 12 18 21

preliminary Results
Major Bleeding

RR = 1.14
95% CI = 0.74-1.75
P = 0.56

Cumulative Risk

No. at Risk
ASA: 2791, 2744, 2572, 2152, 1570, 642, 340
Apix: 2809, 2763, 2567, 2123, 1521, 622, 357

preliminary Results
Study Design

Atrial Fibrillation

**Rivaroxaban**
- 20 mg daily
- 15 mg for Cr Cl 30-49 ml/min

**Warfarin**
- Randomize Double Blind / Double Dummy (n ~ 14,000)
- INR target - 2.5 (2.0-3.0 inclusive)

Monthly Monitoring Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes OR
- Stroke, TIA or Systemic embolus

At least 2 or 3 required*
### Primary Efficacy Outcome

**Stroke and non-CNS Embolism**

Event Rates are per 100 patient-years

Based on Protocol Compliant on Treatment Population

<table>
<thead>
<tr>
<th>Days from Randomization</th>
<th>No. at risk: Rivaroxaban</th>
<th>No. at risk: Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6958</td>
<td>7004</td>
</tr>
<tr>
<td>120</td>
<td>6211</td>
<td>6327</td>
</tr>
<tr>
<td>240</td>
<td>5786</td>
<td>5911</td>
</tr>
<tr>
<td>360</td>
<td>5468</td>
<td>5542</td>
</tr>
<tr>
<td>480</td>
<td>4406</td>
<td>4461</td>
</tr>
<tr>
<td>600</td>
<td>3407</td>
<td>3478</td>
</tr>
<tr>
<td>720</td>
<td>2472</td>
<td>2539</td>
</tr>
<tr>
<td>840</td>
<td>1496</td>
<td>1538</td>
</tr>
<tr>
<td>960</td>
<td>634</td>
<td>655</td>
</tr>
</tbody>
</table>

**Event Rates**

- Rivaroxaban: Event Rate 1.71%
- Warfarin: Event Rate 2.16%

**HR (95% CI)**: 0.79 (0.66, 0.96)

**P-value Non-Inferiority**: <0.001

**P-value for superiority**: N.S.
Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

**Inclusion risk factors**
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF < 40%
- Diabetes mellitus
- Hypertension

**Randomize**
- double blind, double dummy
- (n = 18,201)

**Apixaban** 5 mg oral twice daily
- (2.5 mg BID in selected patients)

**Warfarin** (target INR 2-3)
- Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

**Primary outcome**: stroke or systemic embolism

**Hierarchical testing**: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

**Major exclusion criteria**
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine
Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism

- **Apixaban**: 212 patients, 1.27% per year
- **Warfarin**: 265 patients, 1.60% per year

HR 0.79 (95% CI, 0.66–0.95); P (superiority)=0.011

No. at Risk

- **Apixaban**: 9120, 8726, 8440, 6051, 3464, 1754
- **Warfarin**: 9081, 8620, 8301, 5972, 3405, 1768

P (non-inferiority)<0.001

21% RRR
Stroke or systemic embolism

HR (95% CI)

- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
- Rivaroxaban 20 mg o.d.
- Apixaban 5 mg b.i.d.

De Caterina R, Husted S, Wallentin L et al.

JACC Vol. 59, No. 16, 2012
April 17, 2012:1413-25
De Caterina R, Husted S, Wallentin L et al.
Less intracranial bleeding (consistently)

- **RE-LY**
  - Dabigatran 150 mg
  - Dabigatran 110 mg

- **ROCKET AF**
  - Warfarin 20 mg
  - Warfarin 5 mg

- **ARISTOTLE**
  - Rivaroxaban
  - Apixaban

Major bleed (%/year)

- *P < 0.05 vs warfarin

Intracranial haemorrhage (%/year)

Prognostic implication of ICH

<table>
<thead>
<tr>
<th>Event</th>
<th>Ischemic Stroke</th>
<th>Hemorrhagic Stroke</th>
<th>Subdural Hemorrhage</th>
<th>Extracranial Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighting</td>
<td>1.00</td>
<td>3.00</td>
<td>0.64</td>
<td>0.63</td>
</tr>
</tbody>
</table>
Figure 1 Choice of anticoagulant

Atrial fibrillation

Valvular AF*

Yes

No (i.e. non-valvular AF)

< 65 years and lone AF (including females)

Assess risk of stroke (CHA₂DS₂-VASc score)

0

1**

≥2

Oral anticoagulant therapy

Assess bleeding risk (HAS-BLED score)
Consider patient values and preferences

No antithrombotic therapy

NOAC

VKA

* Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or – less effectively – aspirin only, may be considered in patients who refuse any OAC.

Colour: CHA₂DS₂-VASc score; green = 1, blue = 2, red = ≤2. Line: Solid: best option; Dashed: alternative option.

If absolute contraindications to any OAC or anti-platelet therapy, left atrial appendage closure device can be considered.

AF = atrial fibrillation; CHA₂DS₂-VASc = see text; HAS-BLED = see text; NOAC = novel anticoagulants; VKA = vitamin K antagonist.
Figure 1. Cumulative Incidence of the Primary Efficacy End Point.

## Features of novel oral anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;1,3&lt;/sup&gt;</th>
<th>Edoxaban&lt;sup&gt;4-6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>IIa (thrombin)</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Hours to Cmax</strong></td>
<td>1.25-3</td>
<td>2-4</td>
<td>3-4</td>
<td>1-2</td>
</tr>
<tr>
<td><strong>CYP metabolism</strong></td>
<td>None</td>
<td>32%</td>
<td>Minimal</td>
<td>&lt;4%</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6%</td>
<td>80%</td>
<td>60%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Transporters</strong></td>
<td>P-gp</td>
<td>P-gp/BCRP</td>
<td>P-gp/BCRP</td>
<td>P-gp</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>35%</td>
<td>93%</td>
<td>87%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>14-17 h</td>
<td>7-11 h</td>
<td>8-15 h</td>
<td>8-10 h</td>
</tr>
<tr>
<td><strong>Renal elimination</strong></td>
<td>80%&lt;sup&gt;*&lt;/sup&gt;</td>
<td>33%&lt;sup&gt;#&lt;/sup&gt;</td>
<td>25%&lt;sup&gt;#&lt;/sup&gt;</td>
<td>35%&lt;sup&gt;#&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

BCRP, breast cancer resistance protein  
CYP, cytochrome P450; P-gp, P-glycoprotein  
NR, not reported  

<sup>*</sup>Of absorbed substance  
<sup>#</sup>Of ingested substance

eCrCl

• > 50 mL/min
• 30-50 mL/min
• <30 mL/min
## New Oral Anticoagulants and Coagulation Testing: Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Coagulation assays</th>
</tr>
</thead>
</table>
| Dabigatran | • aPTT – non linear dose response  
• Thrombin time (TT) - too sensitive  
• Ecarin Clotting Time (ECT) - good linearity $$, availability, standardization are limiting factors  
• Hemoclot® assay - best linearity across therapeutic range |
| Rivaroxaban | • PT – best dose response, varies with instrument/reagent combinations  
• INR – non linear dose response, varies with instrument/reagent combinations  
• Anti-Xa assay – with specific Riva calibrator |
| Apixaban | • PT (INR) – non linear dose response  
• Anti-Xa assay - with specific Apixa calibrator |
Reversal of bleeding
Anticoagulation Reversal: Available Agents

- Fresh frozen plasma (FFP)
- Prothrombin Complex Concentrate (PCC)
- Factor VIII Inhibitor Bypassing Activity or aPCC (FEIBA)
- Recombinant activated factor VII (rVIIa)

Common non-specific mechanism of action: enhance thrombin generation and fibrin formation
Anticoagulation Reversal

• Fresh frozen plasma (FFP)

FFP is the plasma separated from whole blood used to replace coagulation factors.

Contains an average of 1 UI/mL of all coagulation proteins, including FV and FVIII and fibrinogen.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Species</th>
<th>Model</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran Etexilate</td>
<td>Mouse</td>
<td>In vivo, intracerebral hemorrhage</td>
<td>Reduced hematoma expansion, no effect on mortality</td>
</tr>
<tr>
<td>Dabigatran, Rivaroxaban</td>
<td>Human</td>
<td>Patients treated with DOA</td>
<td>No data available on reversal of bleeding</td>
</tr>
</tbody>
</table>
**Anticoagulation Reversal: Prothrombin complex concentrates**

- **Non-activated:**
  - ‘4-factor-concentrates’ contain Factors II, VII, IX, and X (e.g. Beriplex, Octaplex, Proplex T, Cofact)
  - ‘3-factor-concentrates’ contain lower amounts of Factor VII (e.g. Prothrombinex-HT, Profilnine, Bebulin)

- **Activated:**
  - FEIBA VH contains Factors II, IX, X and protein C mainly in non-activated forms and Factor VII mainly in the activated form
Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate

A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc; Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD

(Circulation. 2011;124:00-00.)

4 Circulation October 4, 2011
TF/FVIIa → FIX → FIXa
FX → FVIIIa → FXa → FVa → thrombin

Prothrombin Complex Concentrates

Platelet activation
Anti-fibrinolysis
Fibrinogen

Thrombin activates protein C, anticoagulation, anti-fibrinolysis

Inflammation

Protein C pathway activators:
APC, drotrecogin, sTM

FXa inhibitors:
Vitamin K antagonists + Indirect: UFH, LMWH, fondaparinux, idraparinux
Direct: oral (xabans): razaxaban, rivaroxaban, apixaban, DU 176-b, LY 5157117, YM 150

Thrombin inhibitors:
Vitamin K antagonists + Indirect: UFH, LMWH
Direct: parenteral: melagatran, argatroban, hirudins
oral: ximelagatran, dabigatran etexilate

Vitamin K antagonists
Tissue factor pathway inhibitors:
rTFPI
NAPc2
rFVIIiai (ASIS)
TF MoAb, tifagosin

Vitamin K antagonists
FIXa inhibitors: TTP 889

De Caterina et al. ESC WG 18 Task Force on Anticoagulants in Heart Disease - EHJ 2007; 28: 880-913
Case reports are emerging

- Successful bleeding management and/or dabigatran removal in patients receiving dabigatran for stroke prevention in AF
  - More data required to confirm findings

<table>
<thead>
<tr>
<th>Setting</th>
<th>Bleeding control/ removal achieved with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe bleeding following cardiac surgery¹</td>
<td>• High-dose rFVIIa, haemodialysis</td>
</tr>
<tr>
<td>Bleeding associated with non-specific gastritis²</td>
<td>• FFP, packed RBCs</td>
</tr>
<tr>
<td>Spontaneous gross haematuria³</td>
<td>• FFP</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>• Packed RBCs, PCC, haemodialysis⁴</td>
</tr>
<tr>
<td></td>
<td>• FFP, PCC⁵</td>
</tr>
<tr>
<td></td>
<td>• FFP, platelets, cryoprecipitate, packed RBCs, FVIIa, haemodialysis⁶</td>
</tr>
<tr>
<td>Coagulopathy after surgery for aortic intramural haematoma⁷</td>
<td>• IV homologous plasma, cryoprecipitate, PCC, FVIIa</td>
</tr>
<tr>
<td>Removal prior to surgery⁸,⁹</td>
<td>• Haemodialysis</td>
</tr>
</tbody>
</table>

Note: management strategy was at physicians discretion and may not align with dabigatran summary of product characteristics

FFP = fresh frozen plasma; FVIIa = activated Factor VII; IV = intravenous; PCC = prothrombin complex concentrate; RBCs = red blood cells

Anticoagulation Reversal: Recombinant activated factor VII (rVIIa)

rVIIa binds to the TF that is found on the surface of subendothelial cells, activates FIX and FX and leads to the formation of a small amount of thrombin

Thrombin activates platelets and FV and FVIII, resulting in “thrombin burst”

It is used as a bypassing agent for the treatment of bleeding episodes of hemophiliac patients with inhibitors
## rFVIIa for the Reversal of the NOAs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Species</th>
<th>Model</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran Etexilate</td>
<td>Mouse</td>
<td>In vivo, intracerebral hemorrhage</td>
<td>Not effective on the prevention of hematoma expansion</td>
</tr>
<tr>
<td>Dabigatran Etexilate</td>
<td>Rat</td>
<td>In vivo, bleeding time</td>
<td>Reduction of bleeding time; correction of PT, not of aPTT, TT, ECT</td>
</tr>
<tr>
<td>Dabigatran Etexilate</td>
<td>Human, healthy volunteers</td>
<td>Ex vivo, thromboelastography assay</td>
<td>Effective reduction of clot initiation time</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Baboons, rats</td>
<td>In vivo, bleeding time</td>
<td>Reversal of prolonged bleeding time</td>
</tr>
<tr>
<td>Dabigatran, Rivaroxaban</td>
<td>Human</td>
<td>Patients treated with NOA</td>
<td>?</td>
</tr>
</tbody>
</table>
Guidance on the Emergent reversal of Oral Thrombin and Factor Xa Inhibitors

<table>
<thead>
<tr>
<th>Suggestions for Reversal of New Oral Anticoagulants</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral activated charcoal</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hemoperfusion with activated charcoal</td>
<td>Possible</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Activated factor VIIa</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>3-factor PCC</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>4-factor PCC</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Kaatz et al, Am J Hematol 2012: 87,S141
Reversal - Antidotes

- For dabigatran: a monoclonal antibody – in development
Reversal of dabigatran: dabigatran-specific agent

- Antibody clone 22:
  - Highly potent and specific binding to dabigatran
  - Complete inhibition of anticoagulant activity in human plasma, whole blood and \textit{ex vivo} studies

- Potent and selective reversal without affecting normal haemostasis

- Currently under further development

van Ryn et al. ACC 2011; abstract 1142–367
A Specific Antidote for Direct Factor Xa Inhibitor
r-Antidote: a recombinant human fXa variant lacking the membrane binding Gla-domain and active site serine

PRT064445 (r-Antidote)
- Unable to assemble into the prothrombinase complex and cleave prothrombin
- Retained binding ability for all fXa inhibitors
r-Antidote completely reverses the activity of rivaroxaban *in vitro* and *ex vivo*

**In vitro in plasma**

- Human plasma + rivaroxaban (230nM)
- Rat plasma + rivaroxaban (230nM)

**Ex vivo in rat model**

- Infusion of Rivaroxaban (0.25 mg/kg/hr)
- Bolus + Infusion of PRT064445 (4 mg + 4 mg/hr)

![Graphs showing anti-Xa activity and INR levels over time](image)

*P-value ≤ 0.01 (PRT064445 vs. Rivaroxaban Alone)*
r-Antidote completely reverses the activity of apixaban and betrixaban.
In summary (conclusions)

- We are in an extremely exciting phase of developments of new anticoagulants, likely replacing warfarin in most (not all!) indications
- As experience is being accrued, we recognize new challenges, needing new approaches
- All doctors and partners in laboratory medicine and the industry should be aware of these new challenges, to best exploit the potential of the new agents, not underestimating new problems and new needs
Grazie!
Thank you!