Novel oral anticoagulants: mechanisms of action and therapeutic indications

Raffaele De Caterina

“G. d’Annunzio” University – Chieti and “G. Monasterio” Foundation – Pisa, Italy
Co-author ESC Guidelines on Atrial Fibrillation 2010-2012

Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE-AF, Re-DUAL PCI

Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck
Why talking about clinical trials to basic scientists

Bench    Bedside
Agenda

- The history of oral anticoagulation
- The NOAC revolution
- Highlights from clinical trials: from bedside to bench
  - Once day vs twice day
  - Intracranial hemorrhage
  - New treatment indications
Agenda

- The history of oral anticoagulation
Oral anticoagulants: warfarin

- **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
Eisenhower’s Billion-Dollar Heart Attack — 50 Years Later

Franz H. Messerli, M.D., Adrian W. Messerli, M.D., and Thomas F. Lüscher, M.D.

Dr. Paul Dudley White and Former President Dwight D. Eisenhower, 1963.
General mechanisms of coagulation and targets of anticoagulants (Section I)

Position Paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease

Antiplatelet drugs vs warfarin in stroke prevention in atrial fibrillation

Hart, R et al., Ann Intern Med. 2007;146:857-867
Adjusted odds ratios for ischaemic stroke and intracranial bleeding in relation to INR

International normalized ratio

Adapted from Hylek EM. N Engl J Med 1996;335:540-6
The Risk of Ischemic Stroke “Without” OAC Exceeds the Risk of Intracranial Bleeding “With” OAC*

Relation between risk scores and annual event rates of ischemic stroke and ICH in relation to use of oral anticoagulation in 159,013 Swedish AF patients followed up for 1.5±1.1 years (2005–2008)

*Except those with a very low risk of stroke
OAC = oral anticoagulants; ICH = intracranial hemorrhage

**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), \( p=0.0003 \)

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Clopidogrel + ASA</th>
<th>Oral VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3,335</td>
<td>3,371</td>
</tr>
<tr>
<td>0.5</td>
<td>3,152</td>
<td>3,221</td>
</tr>
<tr>
<td>1.0</td>
<td>2,389</td>
<td>2,458</td>
</tr>
<tr>
<td>1.5</td>
<td>927</td>
<td>924</td>
</tr>
</tbody>
</table>

### 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%

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

Specific drugs reported
- acetaminophen
- alcohol
- allopurinol
- aminosalicylic acid
- amiodarone HCl
- amoxicillin
- atorvastatin
- azithromycin
- bivalirudin
- capecitabine
- celamandole
- celecoxib
- cefazolin
- cefoperazone
- cefotetan
- cefoxitin
- ceftriaxone
- cefuroxime
- cerivastatin
- chenodiol
- chloramphenicol
- chloral hydrate
- chlorpropamide
- cholestyramine
- cimetidine
- ciprofloxacin
- clarithromycin
- clofibrate
- colchicine
- COMUDAN overdose
- cyclophosphamide
- danazol
- dextran
- dextrothyroxine
- diazoxide
- diclofenac
- dicumarol
- diflunisal
- disulfiram
- doxycycline
- erythromycin
- esomeprazole
- ezetimibe
- fenofibrate
- fenoprofen
- fluconazole
- fluorouracil
- fluoxetine
- flutamide
- fluvalastin
- fluvoxamine
- gatifloxin
- gentamycin
- glucagon
- halothane
- heparin
- ibuprofen
- ilmepenem
- indomethacin
- influenza virus vaccine
- itraconazole
- ketoprofen
- ketorolac
- lansoprazole
- naproxen
- levamisole
- levofloxacin
- levotyroxine
- liothyronine
- lovastatin
- melencarin acid
- methimazole
- methylidopa
- metilphenidate
- methylsalicylate
- omeprazole
- oxacillin
- oxaprazin
- oxymetholone
- paniprazole
- penicillin G, intravenous
- penicillin G, intramuscular
- phenylbutazone
- phenytoin
- piperacillin
- propranolol
- propafenone
- propylenephene
- propranolol
- propyridiatracil
- quinidine
- quinine
- rabeprazole
- ranitidine
- rofecoxib
- salbutamol
- simvastatin
- stanozolol
- streptokinase
- sulfamethoxazole
- sulfadiazine
- sulindac
- tamoxifen
- tetracycline
- thyroid
- ticarcillin
- ticlopidine
- tissue plasminogen activator (t-PA)
- tolbutamide
- tramadol
- trimethoprim/sulfamethoxazole
- urokinase
- valdecoxib
- valproate
- vitamin E
- zafirlukast
- zileuton

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

www.rxlist.com/cgi/generic/warfarin_ad.htm
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

- there was still a need for safe, effective, oral anticoagulants that do not require monitoring
## Novel Vitamin K Antagonists

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>Dosing</th>
<th>Half-life (hours)</th>
<th>Metabolism</th>
<th>Drug Interactions</th>
<th>Clearance</th>
<th>Phase of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATI-5923 (Tecarfarin)</td>
<td>Oral</td>
<td>Variable, 1X daily</td>
<td>119</td>
<td>Cellular esterases</td>
<td>No P450 metabolism. Less or no drug interactions</td>
<td>100% liver</td>
<td>Phase II study completed</td>
</tr>
</tbody>
</table>
De Caterina et al. ESC WG 18 Task Force on Anticoagulants in Heart Disease – EHJ 2007; 28: 880-913
Thrombin inhibitors

**Indirect**

- UFH
- Exosite 2
- AT

**Direct**

- Hirudin, bivalirudin
- Argatroban, melagatran, dabigatran

De Caterina et al. ESC WG 18 Task Force on Anticoagulants in Heart Disease – EHJ 2007; 28: 880-913
Direct thrombin inhibition

- Oral ximelagatran rapidly absorbed and biotransformed to the active form, melagatran
  - Renal excretion
  - Clinical studies demonstrate efficacy with bid dosing
  - No coagulation monitoring required
  - Low potential for drug/food/alcohol interaction
  - Fixed dosing and predictable response

RDC 2005

R. De Caterina
ALAT > 3x ULN

<table>
<thead>
<tr>
<th></th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPORTIF III</td>
<td>0.8%</td>
</tr>
<tr>
<td>SPORTIF V</td>
<td>0.8%</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

Presented at AHA 2003
Dabigatran Etexilate:
A Novel Direct Thrombin Inhibitor

Dabigatran etexilate
Liver Function Test

Cumulative risk of alanine aminotransferase greater than 3x the upper limit of normal vs. time after randomisation.

Ximelagatran and comparator data from AstraZeneca Briefing Document for FDA Advisory Committee Meeting, Sept 10, 2004, page 128
Dabigatran data from PETRO and PETRO-Ex, data on file.
Oral FXa inhibitors, vs. LMWH vs. pentasaccharides

parenteral

LMWH

oral

FXa xabans

FXa

fondaparinux idraparinux

AT

AT

parenteral

oral
Coagulation: an amplifying cascade

Agenda

- The history of oral anticoagulation
- The NOAC revolution
General mechanisms of coagulation and targets of anticoagulants (Section I)

Position Paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease

### 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

Having more effective or safer anticoagulants was not the original hypothesis for their development. The original hypothesis was to find “non-inferior” agents compared with warfarin, with better acceptance because of the lack of need for frequent coagulation testing.
Can NOACs in SPAF offer a better risk-benefit profile?
NOACs in atrial fibrillation - Timelines

2009
RE-LY
August 2009

2010
AVERROES
February 2011

2011
ROCKET-AF
August 2011
ARISTOTLE
August 2011

2012

2013
ENGAGE-AF
November 2013
New Anticoagulant Therapies Compared to Warfarin: Stroke or Systemic Embolism

This chart may not be reproduced for other internal training or for external use.

New Anticoagulant Therapies Compared to Warfarin: Major Bleeding

Dabigatran 150 mg BID
HR 0.93 (95% CI, 0.81 to 1.07)

Dabigatran 110 mg BID
HR 0.80 (95% CI, 0.70 to 0.93)

Rivaroxaban 20 mg QD
HR 1.04 (95% CI, 0.90 to 1.20)

Apixaban 5 mg BID
HR 0.69 (95% CI, 0.60 to 0.80)

Edoxaban 60 mg QD
HR 0.80 (95% CI, 0.71 to 0.91)

Edoxaban 30 mg QD
HR 0.47 (95% CI, 0.41 to 0.55)

This chart may not be reproduced for other internal training or for external use.

New Anticoagulant Therapies Compared to Warfarin: All-Cause Mortality

![Chart showing comparison of anticoagulant therapies to warfarin based on all-cause mortality.](chart_image)

**Study Drug Better**
- Dabigatran 150 mg BID
  - Hazard Ratio: HR 0.88 (95% CI, 0.77 to 1.00)
- Dabigatran 110 mg BID
  - Hazard Ratio: HR 0.91 (95% CI, 0.80 to 1.03)
- Rivaroxaban 20 mg QD
  - Hazard Ratio: HR 0.92 (95% CI, 0.82 to 1.03)
- Apixaban 5 mg BID
  - Hazard Ratio: HR 0.89 (95% CI, 0.80 to 0.998)
- Edoxaban 60 mg QD
  - Hazard Ratio: HR 0.92 (95% CI, 0.83 to 1.01)
- Edoxaban 30 mg QD
  - Hazard Ratio: HR 0.87 (95% CI, 0.79 to 0.96)

**Warfarin Better**
- Dabigatran 150 mg BID
- Dabigatran 110 mg BID
- Rivaroxaban 20 mg QD
- Apixaban 5 mg BID
- Edoxaban 60 mg QD
- Edoxaban 30 mg QD

---


This chart may not be reproduced for other internal training or for external use.
New Anticoagulant Therapies Compared to Warfarin: Intracranial Hemorrhage

![Graph showing hazard ratios for different anticoagulants compared to warfarin.]


This chart may not be reproduced for other internal training or for external use.
NCB (95% CI) of all treatment arms vs warfarin for the composite outcome including ischemic stroke + systemic embolism + myocardial infarction + hemorrhagic stroke + adjusted major bleeding


<table>
<thead>
<tr>
<th>NOACs</th>
<th>IS equivalent (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>dabigatran 150</td>
<td>-1.02 (-1.56; -0.48)</td>
<td>98</td>
</tr>
<tr>
<td>dabigatran 110</td>
<td>-0.82 (-1.37; -0.27)</td>
<td>122</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>-0.74 (-1.29; -0.17)</td>
<td>135</td>
</tr>
<tr>
<td>apixaban</td>
<td>-1.36 (-1.80; -0.92)</td>
<td>73</td>
</tr>
<tr>
<td>edoxaban 60</td>
<td>-1.04 (-1.48; -0.61)</td>
<td>96</td>
</tr>
<tr>
<td>edoxaban 30</td>
<td>-1.29 (-1.72; -0.86)</td>
<td>77</td>
</tr>
</tbody>
</table>
Agenda

- The history of oral anticoagulation
- The NOAC revolution
- Highlights from clinical trials: from bedside to bench
  - Once day vs twice day
Once vs twice daily – an important choice!

- The choice of the dose and regimen of administration is crucial in drug development.
- Dose selection has to consider all elements maximizing efficacy while preserving safety.
- It is selected in phase II studies – ideally, but not always – in the same patient population to whom the drug should be given.
- Everything else being equal, patient’s convenience (e.g., once daily dosing) is taken into account, as it increases adherence.
- Adherence to the selected drug dosing is a major factor in the difference between a registration clinical trial and the actual post-marketing use of the drug.
Influence of PK and PD parameters on dosing regimens

- The pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of the new oral anticoagulants provide the opportunity for either od or bid dosing.

- Determination of the optimal dosing regimen must be based on assessment of benefit (reduction in thrombotic events) versus risk (increase in bleeding events) in clinical studies.
Rivaroxaban dosing od vs bid

Mueck et al, 2008
No doubts that in AF patients compliance to therapy is better with OD than with BID dosing.

**CONCLUSION**

This large population-based study of >10,000 patients, based on real-world data, indicates that nonvalvular AF patients treated with q.d. dosing regimens for chronic medications were associated with approximately a 26% higher likelihood of adherence compared with subjects on b.i.d. regimens. The findings were consistent across two methods of determining medication adherence.
Edoxaban phase II dose finding study in atrial fibrillation: exposure and bleeding

AUC, area under the plasma concentration-time curve from 0 to 24 hours at steady-state;
$C_{\text{max}}$, maximum steady-state plasma concentration;
$C_{\text{min}}$, minimum steady-state concentration;
QD, once daily;
BID, twice daily

Weitz et al. Thromb Haemost 2010;104:633-41
RUBY-1: cumulative risk of major and clinically relevant non-major bleeding and any bleeding events at 6 months (safety analysis set)

CRNM, clinically relevant non-major
BID, twice daily; QD, once daily

Steg et al. Eur Heart J 2011;32:2541–4
Therefore (conclusions):

- OD therapy in long-term stroke prevention in atrial fibrillation:
  - Appears to be as effective as BID
  - Appears to be as safe as BID
  - It might actually be safer than BID (indirect evidence from other anticoagulants)
  - It is certainly more appealing for the patient
Agenda

- The history of oral anticoagulation
- The NOAC revolution
- Highlights from clinical trials: from bedside to bench
  - Once day vs twice day
  - Intracranial hemorrhage
New Anticoagulant Therapies Compared to Warfarin: Intracranial Hemorrhage

Dabigatran 150 mg BID
HR 0.41 (95% CI, 0.28 to 0.60)

Dabigatran 110 mg BID
HR 0.30 (95% CI, 0.19 to 0.45)

Rivaroxaban 20 mg QD
HR 0.67 (95% CI, 0.47 to 0.93)

Apixaban 5 mg BID
HR 0.42 (95% CI, 0.30 to 0.58)

Edoxaban 60 mg QD
HR 0.47 (95% CI, 0.34 to 0.63)

Edoxaban 30 mg QD
HR 0.30 (95% CI, 0.21 to 0.43)


This chart may not be reproduced for other internal training or for external use.
General mechanisms of coagulation and targets of anticoagulants (Section I)

Position Paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease

Why is warfarin more dangerous than NOACs as to intracranial hemorrhage?

- Warfarin interferes with the formation of a gamma-carboxylated bioactive form of Factor VII
- Factor VII is a crucial mediator of tissue-factor initiated coagulation (the extrinsic pathway)
- The brain is extremely rich in tissue factor, possibly («teleologically») aimed at preventing the catastrophic occurrence of intracerebral bleeding
- By interfering with this pathway, warfarin has a high risk of intracranial hemorrhage, a risk not shared by NOACs
Agenda

- The history of oral anticoagulation
- The NOAC revolution
- Highlights from clinical trials: from bedside to bench
  - Once day vs twice day
  - Intracranial hemorrhage
- New treatment indications – coronary artery disease
A P2Y\textsubscript{12} inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.

- Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications, for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).

- Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.

- Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.
Why adding an anticoagulant long-term?
Warfarin + ASA versus ASA alone:

- Reduces death/MI/stroke only when the correct therapeutic dose is applied (INR 2.0–3.0)
- Increases the risk of major bleeding events

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CI, confidence interval; CV, cardiovascular; INR, international normalized ratio; MI, myocardial infarction; OR, odds ratio.

A new era in anticoagulation

APPRAISE-2: Primary efficacy outcome (CV death, MI, stroke)

Hazard ratio with apixaban, 0.95 (95% CI, 0.80–1.11); P=0.50

No. at Risk
- Apixaban: 3705, 3356, 3048, 2799, 2552, 2312, 2025, 1739, 1525, 1277, 1021, 797, 561, 390, 254, 154
- Placebo: 3687, 3316, 3014, 2751, 2537, 2272, 2030, 1728, 1495, 1248, 987, 803, 571, 412, 267, 164

ATLAS ACS 2–TIMI 51: Primary efficacy outcome (CV death, MI, stroke)

![Graph showing the comparison between Placebo and Rivaroxaban on the primary efficacy outcome.](#)

**Death from Cardiovascular Causes, Myocardial Infarction, or Stroke (%)**

<table>
<thead>
<tr>
<th>Days</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>90</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>180</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>270</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>360</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>450</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>540</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>630</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>720</td>
<td>16</td>
<td>15</td>
</tr>
</tbody>
</table>

**Hazard ratio, 0.84 (95% CI, 0.74–0.96)**

P = 0.008

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>10,229</td>
<td>5,113</td>
</tr>
<tr>
<td></td>
<td>8,817</td>
<td>4,437</td>
</tr>
<tr>
<td></td>
<td>7,797</td>
<td>3,974</td>
</tr>
<tr>
<td></td>
<td>6,324</td>
<td>3,253</td>
</tr>
<tr>
<td></td>
<td>5,137</td>
<td>2,664</td>
</tr>
<tr>
<td></td>
<td>3,967</td>
<td>2,059</td>
</tr>
<tr>
<td></td>
<td>2,830</td>
<td>1,460</td>
</tr>
<tr>
<td></td>
<td>1,747</td>
<td>878</td>
</tr>
<tr>
<td></td>
<td>831</td>
<td>421</td>
</tr>
</tbody>
</table>

ATLAS ACS 2–TIMI 51: rivaroxaban 2.5 mg bid significantly reduced CV events and death

The primary efficacy endpoint reduction was driven by reduced mortality

Both strata. bid, twice daily; CV, cardiovascular; HR, hazard ratio; ITT, intention to treat; MI, myocardial infarction; mITT, modified intention to treat; NNT, number needed to treat.

Rivaroxaban 2.5 mg bid in ATLAS ACS 2–TIMI 51 vs standard antiplatelet therapy showed...

- Greater efficacy, including fewer deaths and reduction in stent thrombosis (not shown)
- An important increase in bleeding, including intracranial haemorrhage (ICH), but without any increase in fatal bleeding or fatal ICH
- Even greater benefits in patients with elevated cardiac biomarkers and without previous stroke/TIA

Difficulties in buying this concept

- Triple therapy in ACS is more complicated than DAPT using ticagrelor (or prasugrel)
- Identifying candidate patients is somewhat complicated
- Clopidogrel perceived as «an old drug»
- Is the lower mortality with rivaroxaban real? «One swallow does not make spring»
- Difficulties in accepting the much higher rates of bleeding
Can we then use rivaroxaban dropping aspirin in CAD?
GEMINI-ACS-1 Study Design

**Objective:** Safety of rivaroxaban versus ASA in addition to either clopidogrel or ticagrelor therapy in patients with a recent ACS

**Population:** Patients with an acute coronary syndrome. The number of patients is approximately 1500.

**Acute phase treatment (invasive or not)**
- Clopidogrel + ASA
- Ticagrelor + ASA

**Maintenance dose of ASA and P2Y12**
- Clopidogrel 75 mg od + ASA 100 mg od
- Ticagrelor 90 mg bid + ASA 100 mg od
- Clopidogrel 75 mg od + rivaroxaban 2.5 mg bid
- Ticagrelor 90 mg bid + rivaroxaban 2.5 mg bid

**Selection up until 10 days prior to R**

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Treatment phase</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 30</td>
<td>Day 90</td>
</tr>
<tr>
<td>Day 180</td>
<td>Day 270</td>
<td>End of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>End of study</td>
</tr>
</tbody>
</table>

De Caterina R and Goto S, Vascul Pharmacol 2016; 81:1-14
COMPASS Study Design

**Objective:** Efficacy and safety of rivaroxaban, low-dose rivaroxaban plus ASA or ASA alone for reducing risk of MI, stroke or CV death in patients with CAD or PAD

**Population:** Patients with CAD or PAD

- Rivaroxaban 2.5 mg bid + ASA 100 mg od
- Rivaroxaban 5.0 mg bid + ASA placebo
- ASA 100 mg od + rivaroxaban placebo

N~27,400

1:1:1

30-day washout period

Final follow-up visit

Final washout period visit
Phase III COMPASS study with Bayer’s Rivaroxaban in Patients with Coronary or Peripheral Artery Disease Shows Overwhelming Efficacy and Meets Primary Endpoint Early
Conclusions

- A very exciting era in cardiology with NOACs, about 70 years after the patenting of warfarin as a rat poison!
Stay tuned!