Anticoagulation

When Things Go Wrong!
Prevention and Management of Bleeding

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Clinical Lead, UCLP

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Clinical Adviser for AF, AHSN Network
Declarations of Interest

• SA has attended advisory boards and / or received speaker honoraria for Bayer, BMS / Pfizer, Daiichi-Sankyo
• SA is chair of iPACT (international Pharmacist for Anticoagulation Care Taskforce)
• SA is medical advisory committee for Atrial Fibrillation Association

• HW has attended advisory boards and / or received speaker honoraria for Bayer, BMS / Pfizer, Daiichi-Sankyo
• HW is secretary of the Primary Care Cardiovascular Society (UK)
• HW is CV lead for the Primary Care Pharmacists Association
Icebreaker

• Who are you?
• Where are you from?
• What is your job role?
• An interesting fact about you...
What do you want to get out of this workshop?

• Each table to come up with 3 key points....
Learning Objectives

• discuss the risk of bleeding on warfarin and DOACs, particularly major and life-threatening bleeds
• understand the use of bleeding risk scores
• identify and address modifiable risk factors for bleeding
• describe the strategies used to manage mild, moderate and life-threatening bleeds, including the available reversal agents
• Be able to explain bleeding risk to patients prescribed anticoagulants and advise patients what action to take in the event of a bleed
Meet Elsie

- 82 year old British woman
- A&E admission for acute HF and “irregular pulse”
  - Prior MI
- Discharged with diagnosis of AF & HF

*Prescribed aspirin given worries about “frailty” ...*
Stroke risk

Anticoagulate!

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristics</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>0</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal liver or renal function</td>
<td>0</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>0</td>
</tr>
<tr>
<td>L</td>
<td>Labile INR</td>
<td>0</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (age &gt; 65)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol</td>
<td>0</td>
</tr>
</tbody>
</table>

Risk score 1

CHA2DS2-VASc Score for Atrial Fibrillation Stroke Risk

Calculate stroke risk for patients with atrial fibrillation, possibly better than the CHADS2 score.

Age?
- < 65 years old -0
- 65-74 years old +1
- > 75 years old +2

Score 5

Stroke risk was 6.7% per year according to Yip et al’s 2010 stroke study and the European Society of Cardiology’s guidelines.
So, what happened next?

A few months later……..

• Admitted with mild dysarthria and right sided facial asymmetry which resolved rapidly = TIA

• Discharged on dipyridamole 200mg and aspirin or switch to warfarin “if GP convinces patient“

**BUT, 5 days later patient re-admitted to A&E and discharged with large left CVA...**

• She remains aphasic with significant right limb spastic paresis and doubly incontinent...
Jim

- Jim is a 76 year old man
- He is generally fit and healthy
- He has a diagnosis of hypertension treated with amlodipine 5mg daily and candesartan 16mg daily
- He is treated for arthritis with ibuprofen
- He is very active and is the main carer for his disabled wife
- He does drink 2-3 units of alcohol (rum) most days of the week
- A routine blood pressure check revealed an irregular pulse
- His BP was recorded as 164/94mmHg
- An ECG confirmed AF
Jim is a 76 year old man
- He is generally fit and healthy
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- He is treated for arthritis with ibuprofen
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- His BP was recorded as 164/94mmHg
- An ECG confirmed AF

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H Hypertension*</td>
<td>1</td>
</tr>
<tr>
<td>A Abnormal renal and liver function</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>E Elderly (eg, age &gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>D Drugs or alcohol (1 point each)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Maximum score</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>
# CHA₂DS₂-VASc / HAS-BLED / EHRA atrial fibrillation risk score calculator

Please select CHADSVASC and HASBLED risk factors, EHRA score and click copy to clipboard to copy and paste in your electronic files.

## Chadsvasc risk factors [click on present risk factors]

<table>
<thead>
<tr>
<th>RISK FACTORS</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>2</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/thrombo-embolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Sex Female</td>
<td>1</td>
</tr>
<tr>
<td>Your score</td>
<td>0</td>
</tr>
</tbody>
</table>

## CHADSVASC clinical risk estimation. Adapted from Lip et al. See Van den Ham et al. below for actual risks in a larger population.

<table>
<thead>
<tr>
<th>CHA₂DS₂-VASc SCORE</th>
<th>PATIENTS (n=7329)</th>
<th>ADJUSTED STROKE RATE (% year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>422</td>
<td>1,3%</td>
</tr>
<tr>
<td>2</td>
<td>1230</td>
<td>2,2%</td>
</tr>
<tr>
<td>3</td>
<td>1730</td>
<td>3,2%</td>
</tr>
<tr>
<td>4</td>
<td>1718</td>
<td>4,0%</td>
</tr>
<tr>
<td>5</td>
<td>1159</td>
<td>6,7%</td>
</tr>
<tr>
<td>6</td>
<td>679</td>
<td>9,8%</td>
</tr>
<tr>
<td>7</td>
<td>294</td>
<td>9,6%</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>6,7%</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>15,2%</td>
</tr>
</tbody>
</table>
## Bleeding risk: HAS-BLED score

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H Hypertension*</td>
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<td>B Bleeding</td>
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<tr>
<td>L Labile INRs</td>
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<td>E Elderly (eg, age &gt;65 years)</td>
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<tr>
<td><strong>Maximum score</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total score</th>
<th>Major bleeds†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>8.70</td>
</tr>
<tr>
<td>≥5</td>
<td>≥12.50</td>
</tr>
</tbody>
</table>

†Annual risk, per 100 patient years

*Uncontrolled hypertension, systolic pressure >160 mmHg

A high HAS-BLED score (≥3) indicates a need for regular clinical review and follow-up, but is not in itself a reason to avoid oral anticoagulation.

INR: International Normalized Ratio
Are the risks and benefits comparable?
The risk of ischaemic stroke ‘without’ OAC exceeds the risk of intracranial bleeding ‘with’ OAC*

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

*Except those with a very low risk of stroke
ICH, Intracranial Haemorrhage; OAC, Oral Anticoagulant

Balancing benefits and risks

• Different perspectives
  • Patients fear strokes\(^1\)
  • Healthcare professionals fear bleeding\(^1,2\)

• Outcomes are very different
  • Many AF strokes are catastrophic (e.g., 60-70% permanent disability, 20% mortality)\(^2\)
  • Most major bleeding is from the GI tract and can usually be managed
  • Intracranial bleeds are the exception

An increased bleeding risk is an unavoidable consequence of stroke prevention!
Are you going to offer Jim anticoagulation?

a. Yes
b. Yes
c. Yes
d. Yes

But reduce his bleeding risk. ...
Review pain control, control hypertension and advise moderation of alcohol to less than 8 units per week.
Stroke Prevention
Anticoagulant Effect

Meta-analysis of stroke or systemic embolism

Category
W vs Placebo
W vs W_{low dose}
W vs Aspirin
W vs Aspirin + Clop
W vs Ximelagatran
W vs Dabigatran 110
W vs Rivaroxaban
W vs Dabigatran 150
W vs Apixaban 5

Relative Hazard Ratio
(95% CI)

0.3 0.6 0.9 1.2 1.5 1.8 2.0

Favours warfarin
Favours Rx

ICH

0 0.3 0.6 0.9 1.2 1.5 1.8 2.0

Major bleeding

0 0.3 0.6 0.9 1.2 1.5 1.8 2.0

Favours warfarin
Favours Rx

Modified from Camm AJ. EHJ 2009;30:2554-5
Major bleeding rates: NOACs vs VKA in phase III trials

<table>
<thead>
<tr>
<th></th>
<th>NOAC %</th>
<th>Warfarin %</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute VTE treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 150¹</td>
<td>1.0</td>
<td>1.6</td>
<td>2.13</td>
<td>0.69–0.80</td>
</tr>
<tr>
<td>Rivaroxaban²</td>
<td>1.0</td>
<td>1.7</td>
<td>0.54</td>
<td>0.37–0.79</td>
</tr>
<tr>
<td>Apixaban³</td>
<td>0.6</td>
<td>1.8</td>
<td>0.31</td>
<td>0.17–0.55</td>
</tr>
<tr>
<td>Edoxaban⁴</td>
<td>1.4</td>
<td>1.6</td>
<td>0.84</td>
<td>0.59–1.21</td>
</tr>
<tr>
<td>Stroke prevention in AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 110⁵,⁶</td>
<td>2.87</td>
<td>3.57</td>
<td>0.80</td>
<td>0.70–0.93</td>
</tr>
<tr>
<td>Dabigatran 150⁵,⁶</td>
<td>3.32</td>
<td>3.57</td>
<td>0.93</td>
<td>0.81–1.07</td>
</tr>
<tr>
<td>Rivaroxaban⁷</td>
<td>3.6</td>
<td>3.4</td>
<td>1.04</td>
<td>0.90–1.20</td>
</tr>
<tr>
<td>Apixaban⁸</td>
<td>2.13</td>
<td>3.09</td>
<td>0.69</td>
<td>0.60–0.80</td>
</tr>
<tr>
<td>Edoxaban high⁹</td>
<td>2.43</td>
<td>2.75</td>
<td>0.80</td>
<td>0.71–0.91</td>
</tr>
<tr>
<td>Edoxaban low⁹</td>
<td>1.61</td>
<td>2.75</td>
<td>0.47</td>
<td>0.41–0.55</td>
</tr>
</tbody>
</table>

For information purposes only, no cross trial comparisons can be drawn – adapted from references

HASBLED Scores in AF trials

62% of patients in ROCKET AF had a very high risk of bleeding
Major bleeding mortality: rivaroxaban vs VKA in clinical practice

<table>
<thead>
<tr>
<th></th>
<th>VKA in daily care&lt;sup&gt;1–7&lt;/sup&gt;</th>
<th>Rivaroxaban in daily care&lt;sup&gt;8&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rates of major bleeding</td>
<td>~6–8/100 patients/year</td>
<td>~3–4*/100 patients/year</td>
</tr>
<tr>
<td>Case-fatality rate of major bleeding</td>
<td>~15%</td>
<td>~6%</td>
</tr>
</tbody>
</table>

*SPAF: 3.1 (95% CI 2.2–4.3); VTE: 4.1 (95% CI 2.5–6.4) events per 100 patient-years

Comparison of Main Outcomes: XANTUS versus ROCKET AF

Not intended for direct comparison as no head to head data available

<table>
<thead>
<tr>
<th>CHADS₂</th>
<th>Prior stroke*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET AF</td>
<td>3.5</td>
</tr>
<tr>
<td>XANTUS</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Includes prior stroke, SE or TIA

XANTUS: Major bleeding rates in real world studies consistent with findings from ROCKET AF

**Clinical Trial**

ROCKET AF  
mean CHADS₂-Score 3.5  
Event rate (%/year) = 7,111

**Retrospective Database**

US DoD PMSS²  
mean CHADS₂-Score 2.2  
Event rate (%/year) = 27,467

**Prospective Registry**

XANTUS³  
mean CHADS₂-Score 2.0  
Event rate (%/year) = 6,784

Results are not intended for direct comparison

*Major bleeding definitions according to ISTH; **Major bleeding and clinically relevant non-major bleeding was defined by the Cunningham algorithm⁴

FDA Medicare analysis findings support the benefit–risk profile of dabigatran shown in RE-LY®

*84% received 150 mg BD, 16% received 75 mg BD.

Primary findings for dabigatran are based on analysis of both 75 mg and 150 mg together without stratification by dose. **In Europe, 75mg BD is not licensed for this indication**


HR = hazard ratio; BD = twice daily; ICH = intracranial haemorrhage; MI = myocardial infarction; GI = gastrointestinal.
‘High risk’?

My patient is too old

My patient has falls

My patient is too frail

My patient has poor renal function

My patient will bleed
The Challenges of Anticoagulation in AF

- Prevalence of AF increases with age
- Age alone is an important risk factor for stroke\(^1,2\)
  - 55+ years: After the age of 55 years, stroke risk doubles for each 10 years of life\(^3\)
- Warfarin reduces stroke risk by \(\sim 60\%\) versus antiplatelet therapy or placebo (N=28,044)\(^4\)
- Major bleeding risk is higher in elderly compared with younger patients taking warfarin (N=472)\(^5\)

Stroke\(^1\)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>2-year incidence (per 1000 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–59</td>
<td>4.1</td>
</tr>
<tr>
<td>60–69</td>
<td>55</td>
</tr>
<tr>
<td>70–79</td>
<td>42.5</td>
</tr>
<tr>
<td>80–89</td>
<td>97.9</td>
</tr>
<tr>
<td>80–89</td>
<td>142.9</td>
</tr>
</tbody>
</table>

Major bleeding\(^5\)

- Age \(\geq 80\) years
- Age <80 years

AF, atrial fibrillation

Older AF patients less likely to get warfarin

BAFTA:

- 2001–2004; 260 GPs in England and Wales
- 973 pts ≥ 75 years (81.5 ± 4.2)
- 72% CHADS$_2$ ≤ 2
- 40% on warfarin, 42% on aspirin
- Warfarin (target INR 2–3) or aspirin (75 mg per day)
- 1º endpoint - fatal or disabling stroke (ischaemic or haemo-rrhagic), other intracranial haemorrhage, or clinically significant arterial embolism

INR > 3.0: 14% of the time


Birmingham Atrial Fibrillation Treatment of the Aged

Event free survival

<table>
<thead>
<tr>
<th>Years after randomisation</th>
<th>Aspirin (A)</th>
<th>Warfarin (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>24 (1.8%)</td>
</tr>
<tr>
<td>1</td>
<td>80</td>
<td>48 (3.8%)</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

RR = 0.48
(0.28–0.80)
p = 0.0027

Stroke:
0.8% vs. 1.8%
RR = 0.30
(0.13–0.63)
p = 0.0004

Intra-cranial haemorrhage on W vs. A:
0.5% vs. 0.4% (RR 1.15, 0.29 – 4.77, n.s.)

Extra-cranial haemorrhage:
1.4% vs. 1.6% (RR 0.87, 0.43 – 1.73, n.s.)
Balancing benefits vs. risks
Are all bleeds equal?

- Hb drop of $\geq 2\, \text{g/dl}$
- Transfusion of $\geq 2\, \text{U}$
- Symptomatic bleeding in critical organ

- Fatal haemorrhage
- Intracranial haemorrhage
- Hb drop of $\geq 5\, \text{g/dl}$
- Transfusion of $\geq 4\, \text{U}$
- Inotropic agent support
- Surgery

My patient will bleed.
Net Clinical Benefit of Rivaroxaban vs Warfarin Is Greater in the Elderly

Net clinical benefit of rivaroxaban compared with warfarin in older and younger patients*

*Based on avoidance of ischaemic stroke, severe (life-threatening) bleeding, and all-cause mortality; \( p \) (interaction) = 0.034 for non-haemorrhagic stroke

Halperin JL et al, Circulation 2014;130:138–146
Real-World Rates of Major Bleeding in an Older Population of Rivaroxaban Users

• Analysis of electronic records from the US DoD
• 31,883 rivaroxaban users, overall major bleeding rate: 2.85%/year

Major bleeding rates generally increased with age; most events occurred in patients aged ≥75 years (74.1%)

Major bleeding incidence rates were similar to those reported in ROCKET AF

US DoD, United Stated Department of Defense
Patients with AF and renal impairment

- Every third patient with AF has chronic kidney disease (CKD)\(^1\)
- Prevalence of both AF and CKD increase with age\(^1\)

Frequency of CKD in AF patients\(^1\)

- Stage I and II: eGFR > 60 mL/min, 67%
- Stage III: eGFR 30-59 mL/min, 30%
- Stage IV: eGFR 15-29 mL/min, 2%
- Stage V: eGFR < 15 mL/min, 1%

Patients with AF and renal impairment

- Are at higher risk of bleeding and stroke than those with normal renal function\(^1\)
- Are more often undertreated with warfarin than those with normal renal function\(^2\)

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![Bar chart showing event rates for stroke or thromboembolism and bleeding in patients with and without renal disease.](chart.png)

**Danish registry\(^1\) (N=132,372)**

- Without renal disease (n=127,884):
  - Event rate/100 person-years: 3.61
  - HR 1.49 (95% CI 1.38-1.59)
  - No statistical significance for HR

- Non-end-stage CKD (n=3587):
  - Event rate/100 person-years: 6.44
  - HR 2.24 (95% CI 2.10-2.38)
  - P<0.001

NOACs (vs Warfarin)
Ischemic Stroke Or Bleeding: Patients With AF And CKD

Safety And Efficacy Of NOACs vs VKA In Patients With Renal Impairment

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild renal impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CrCl [eGFR] 50–79 ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major/NMCR bleeding</td>
<td>0.80 (0.71–0.90)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>0.70 (0.54–0.92)</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Moderate renal impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CrCl [eGFR] 30–49 ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major/NMCR bleeding</td>
<td>0.81 (0.54–1.21)</td>
<td>0.29</td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>0.72 (0.57–0.92)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Favours NOAC  | Favours VKA

Falls – what is the risk?

- Markov decision analysis was used to determine the preferred treatment strategy in patients > 65 yrs old.
- Patients need to fall > 295 times per year for the risk to outweigh the benefit.
- Mean number of falls/year of elderly people: 1.8

Do not withhold anticoagulation solely because the person is at risk of having a fall. NICE 2014

Man-Son-Hing et al Arch Intern Med. 1999;159:677-685
Edoxaban: Outcomes in patients at increased risk of falls

Efficacy and safety of edoxaban vs warfarin in patients with and without risk of falls at baseline

There was no significant interaction by treatment group in patients with vs without an increased risk of falling (all P > 0.05). Patients at risk of falls were at a significant risk of ICH, which was reduced with edoxaban.

ICH=intracranial haemorrhage; SSE=stroke or systemic embolism
Jim

- Jim needs anticoagulation – after discussion he opts for a non-vitamin K oral antagonist as he is the main carer for his disabled wife and is worried about the warfarin monitoring requirements
- CHADS2VASc = 3; HASBLED 4, but reduced to 2 by controlling BP and switching to a simple painkiller
- He is started on rivaroxaban 20mg daily
- He asks about bleeding risk...
- What do the major trials tell us about bleeding risk?
- How will you explain his bleeding risk to him?
Major bleeding rates (% per year)

**RE-LY**  *Connolly NEJM 2009*
- 3.36% warfarin versus 3.11% dabigatran 150 mg bd (NS) / 2.71% dabigatran 110 mg bd (p=0.003)
- Less life threatening bleeds and ICH
- 150mg - more major GI bleeds

**ROCKET AF**  *Patel NEJM 2011*
- 3.4% warfarin versus 3.6% rivaroxaban (NS)
- Reduced ICH and fatal bleeds
- Increased transfusions and more major GI bleeds

**ARISTOTLE**  *Granger NEJM 2011*
- 3.09% warfarin versus 2.13% apixaban (p<0.001)
- Less ICH
- No increased risk of GI bleeds

**ENGAGE AF**  *Giugliano NEJM 2013*
- 3.43% warfarin, 2.75% with high-dose arm edoxaban (p<0.001) and 1.61% with low-dose arm edoxaban (p=<0.001)
- Less life-threatening bleeding, ICH and major bleeding
- More GI bleeds (with high-dose arm)
Reducing risk of bleeding

1. Control BP

2. Review benefit/risk of concomitant aspirin:
   - Hypertensives, diabetics, CHD and no acute ischemic event or intervention in the last year
   - Stop aspirin when INR in therapeutic range

3. Risk of bleeding is greatest in first 90 days of OAC therapy
   - Caution: drug interactions and new drugs
   - Close or more frequent monitoring

4. Review concomitant use of NSAIDS, SSRIs, steroids

5. Consider a PPI

Real world case 1:

• CHADSVASc = 4
  • Risk of stroke = 4.8-6.7% per annum = approx. 38-50% over 10 years
• Anticoagulant stopped in Hospital due to recurrent falls
• On aspirin and clopidogrel

• Active-W study showed that Aspirin and Clopidogrel are inferior to warfarin in stroke prevention but have the same bleed risk
• Has this patient received optimal care?
Falls – what is the risk?

- Markov decision analysis was used to determine the preferred treatment strategy in patients > 65 yrs old.
- Patients need to fall > 295 times per year for risk to outweigh benefit.
- Mean number of falls/year of elderly people: 1.8.

Man-Son-Hing et al Arch Intern Med. 1999;159:677-685

Do not withhold anticoagulation solely because the person is at risk of having a fall. NICE 2014
The risk of ischaemic stroke "without" OAC exceeds the risk of intracranial bleeding "with" OAC*

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


*Except those with a very low risk of stroke
Active W Study
Warfarin vs ASA+clopidogrel

Warfarin (INR 2.0–3.0) vs ASA (75–100 mg) + clopidogrel (75 mg)

- Primary endpoint: Clopidogrel/ASA (n=3,335) vs Warfarin (n=3,371)
  - RR 1.44
  - p=0.0003

- Major bleeding: Clopidogrel/ASA vs Warfarin
  - 2.42 vs 2.21
  - RR 1.10
  - p=0.53

*Stopped after complete enrolment because of warfarin superiority;
**Composite of stroke, non CNS embolism, MI and vascular death

ACTIVE Investigators, Lancet 2006;367:1903-1912
Case 2:

- CHADS2VAsc = 5
  - 7.2 to 10% per annum = 53-65% risk over next 10 years
- Practice discussed and ‘not in best interests of patient’
- Patient continued on aspirin 75mg daily

- Any effort to discuss with patient or carer? This patient is guaranteed to have a stroke without treatment!
- Has this patient received optimal care?
Older AF patients less likely to get warfarin

BAFTA:
- 2001–2004; 260 GPs in England and Wales
- 973 pts ≥ 75 years (81.5 ± 4.2)
- 72% CHADS\textsubscript{2} ≤ 2
- 40% on warfarin, 42% on aspirin
- Warfarin (target INR 2–3) or aspirin (75 mg per day)
- 1\textsuperscript{st} endpoint - fatal or disabling stroke (ischaemic or haemo-rrhagic), other intracranial haemorrhage, or clinically significant arterial embolism

\textit{INR > 3.0: 14% of the time}


Birmingham Atrial Fibrillation Treatment of the Aged

- Event free survival
- \textbf{Aspirin (A)} vs. \textbf{Warfarin (W)}
  - 24 (1.8%) vs. 48 (3.8%)
  - RR = 0.48 (0.28–0.80)
  - Stroke: 0.8% vs. 1.8%
  - RR = 0.30 (0.13–0.63)
  - \( p = 0.0027 \) vs. \( p = 0.0004 \)

- \textbf{Intra-cranial haemorrhage on W vs. A}:
  - 0.5% vs. 0.4% (RR 1.15, 0.29 – 4.77, n.s.)
- \textbf{Extra-cranial haemorrhage}:
  - 1.4% vs. 1.6% (RR 0.87, 0.043 – 1.73, n.s.)
Case 3

• CHADSVASc of 6
  • 9.7%-13.6% risk of stroke per annum = 64-77% risk over 10 years
• PR bleed stopped warfarin in August 2011
• Identified as ‘for anticoag’
• No discussion, but now deemed not a candidate

• Prior bleeding on a/c is not a C/I to future treatment
• Is there a lesion to fix...?
• Has this patient received optimal care?
Figure Legend:

Figure. Time-to-outcome analysis according to resuming warfarin therapy status. A, Thrombosis (P = .002, log-rank test); B, recurrent gastrointestinal tract bleeding (GIB) (P = .10, log-rank test); C, death (P < .001, log-rank test); and D, death including only patients who died at least 7 days after the index GIB (P < .001, log-rank test).
Part 2: Managing Bleeding
PATIENT RECEIVING RIVAROXABAN THERAPY: HAEMORRHAGE PROTOCOL

**STOP: Rivaroxaban**

**Request:**
1. Coagulation screen to include Prothrombin Time (PT) and Anti-Xa assay
   [Important to document time of last dose of rivaroxaban – order 'Rivaroxaban level' on EPR]
2. Full blood count and renal function / eGFR

**MILD BLEED**
- Mechanical compression
- Delay next rivaroxaban dose or discontinue treatment

**MAJOR BLEED**
- Maintain BP and Urine Output
  - Optimise tissue oxygenation
  - Control haemorrhage
    - Mechanical compression
    - Surgical / radiological intervention
  - Tranexamic Acid (1g i.v.)
  - Red cell transfusion
    - Aim Hb > 7 g/dl
  - Platelet transfusion
    - Aim Plt > 50 x 10^9/l or
    - If CNS bleed aim Plt > 100 x 10^9/l
  - Identify bleeding source e.g. surgery, endoscopy, interventional radiology

**LIFE THREATENING BLEED**
- Intravenous Octaplex (PCC) 25 units/kg (obtain from blood bank)
  - Consider repeat dose if no improvement
See Octaplex administration guidance
  - Caution if history of thrombosis, DIC or liver disease

**PT normal**
- PT prolonged
- NO rivaroxaban anticoagulant effect present

**Rivaroxaban anticoagulant effect may be present** (consider oral charcoal if rivaroxaban ingestion <2 hours)

**Continues to bleed**

**Maj or Bleed:** Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome

**Contact Haematology on 736 266 or out of hours via switchboard**
An 81-year-old man from a nursing home referred for atypical chest pain

Past medical history:
- Hypertension
- Moderate cognitive impairment, though still able to do daily tasks and follow orders
- History of falls (almost 2 dozen times in the past year)
- Diagnosed with AF 3 years previously, soon after admission to the home

Physical examination:
- 6'6" (1.98 m) tall, 180 lbs (81.6 kg)
- HR 110 bpm, irreg irreg; BP 144/92 mmHg
- JVP 4 cm, 1+ pitting edema, but chest and heart sounds normal

Medication:
- Amlodipine 20 mg QD, hydrochlorothiazide 25 mg QD, metoprolol 25 mg BID, ASA 325 mg QD (for AF, given bleeding risk concerns)

Investigations:
- CBC, liver function tests, TSH all normal; Creatinine = 85 μmol/L; CrCl = 59 ml/min
- ECG: AF at 99 bpm, otherwise unremarkable
- Echo: LVEF 62%, mild-moderate concentric LVH, increased filing pressures
### Polling Question – Patient CD

<table>
<thead>
<tr>
<th>Is it safe for CD to receive anticoagulant therapy?</th>
<th>A. Yes</th>
</tr>
</thead>
</table>

**Polling Question**

What Oral Anticoagulant At What Dose Would You Start?

- A. Warfarin (INR 2.0 - 3.0)
- B. Apixaban 2.5 mg BID
- C. Dabigatran 110 mg BID
- D. Rivaroxaban 15 mg QD
Risk Of Falls And Major Bleeding

For the calculated risk of subdural hematoma from falling to outweigh the stroke reduction benefit of warfarin, a patient with a 6% annual stroke risk from AF would need to fall 295 times in a year.

Risk of falls is not an adequate reason to avoid oral anticoagulation

Elderly Patients (≥75 Years) With AF: What Do We Know About Treating Them With NOACs?

**Breakdown Of Elderly Patients In Pivotal Trials**

<table>
<thead>
<tr>
<th></th>
<th>ARISTOTLE</th>
<th>ENGAGE-AF</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>70</td>
<td>72</td>
<td>N/S</td>
<td>73</td>
</tr>
<tr>
<td>Mean CHADS$_2$ Score</td>
<td>2.1</td>
<td>2.8</td>
<td>2.2</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Efficacy And Safety Of The NOACs In The Elderly

The Relative Efficacy And Safety Of NOACs vs Warfarin Is Consistent In Elderly Patients (>75 Years)

Pooled Stroke and Systemic Embolism Events According to Age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Pooled NOAC (Events)</th>
<th>Pooled Warfarin (Events)</th>
<th>RR (95% CI)</th>
<th>P-value (int.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75</td>
<td>496/18073</td>
<td>578/18004</td>
<td>0.85 (0.73–0.99)</td>
<td>0.38</td>
</tr>
<tr>
<td>≥75</td>
<td>415/11188</td>
<td>532/11095</td>
<td>0.78 (0.68–0.88)</td>
<td></td>
</tr>
</tbody>
</table>

Pooled Major Bleeding Events According to Age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Pooled NOAC (Events)</th>
<th>Pooled Warfarin (Events)</th>
<th>RR (95% CI)</th>
<th>P-value (int.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75</td>
<td>1317/18460</td>
<td>1543/18396</td>
<td>0.79 (0.67–0.94)</td>
<td>0.28</td>
</tr>
<tr>
<td>≥75</td>
<td>1328/10771</td>
<td>1346/10686</td>
<td>0.93 (0.74–1.17)</td>
<td></td>
</tr>
</tbody>
</table>

# Age, Major Bleeding And Dabigatran

## Event rate (%/year)\(^1\)

<table>
<thead>
<tr>
<th>Age</th>
<th>D110</th>
<th>D150</th>
<th>Warfarin</th>
<th>D110 vs warfarin</th>
<th>D150 vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>0.82</td>
<td>0.89</td>
<td>2.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>2.29</td>
<td>2.60</td>
<td>3.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>4.43</td>
<td>5.10</td>
<td>4.37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(p_{	ext{Interaction}}\) 0.0003\(^*\)  0.0001\(^*\)

## Dabigatran 150 mg dose:
- Avoid absolutely in patients ≥80 years old\(^2\)
- Consider avoiding in patients ≥75 years old when the thromboembolic risk is low and the bleeding risk is high\(^2\)

For both rivaroxaban and apixaban, efficacy against stroke and safety for avoiding major hemorrhage is not significantly different between patients ≥75 years vs those <75 years\(^3,4\)

*Interaction with age was seen for major extracranial bleeding but not for intracranial bleeding

Dose Prescribing Of Apixaban

Apixaban

Patient has risk factor for stroke

- Estimate CrCl
  - <15 mL/min
    - Not recommended
  - 15–29 mL/min
    - 2.5 mg BID
  - ≥30 mL/min
    - Check age
      - ≥80
    - Check weight
      - ≥60 kg
    - Check serum creatinine
      - >133 μmol/L

If ≥2 features
- 2.5 mg BID
If ≤1 feature
- 5 mg BID

CD

Apixaban SmPC
Dose Prescribing Of Dabigatran

Dabigatran

Patient has risk factor for stroke

Estimate CrCl

<30 mL/min

Contraindicated

Age >80

110 mg BID

Age ≥75 or high risk for bleeding

110 mg BID

Age <75

150 mg BID

Age 75–80

150 mg BID

Age >80

110 mg BID

>50 mL/min

Low thromboembolic risk and high bleeding risk

CD

Dabigatran SPC, July 2014.
Rivaroxaban is to be used with caution in patients with CrCl 15–29 mL/min
Rivaroxaban SPC, January 2014
Case – Patient EF

- A 79-year-old widow presents with intermittent palpitations over several years that have now become more persistent and therefore worrisome to her

- Past medical history:
  - T2DM with neuropathy and retinopathy
  - Longstanding hypertension
  - Osteoarthritis
  - Depression (since death of husband)

- Physical examination:
  - 5’4” (1.63 m) tall, 134 lbs (61.0 kg)
  - HR 112 bpm, irreg irreg; BP 130/70 mmHg
  - Chest clear
  - Variable S1, no A-wave on JVP, otherwise unremarkable

- ECG:
  - Atrial fibrillation at 104 BPM, nonspecific ST-T changes (AF never before documented; new 24-hour holter shows recurrent episodes, lasting several minutes during the day but up to 2 hours overnight)

| Medications       | Amitriptyline 10 mg at hs
|                   | Gabapentin 200 mg TID
|                   | Metformin 500 mg BID
|                   | HCTZ 25 mg QD
|                   | Perindopril 4 mg QD
|                   | Loperamide prn
|                   | OTC NSAID prn

| Allergies         | Sulfa, wasp stings

<table>
<thead>
<tr>
<th>Bloodwork</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Hemoglobin</td>
</tr>
<tr>
<td>Hb A$_1$$C$</td>
</tr>
<tr>
<td>Electrolytes</td>
</tr>
<tr>
<td>TSH</td>
</tr>
</tbody>
</table>

Note: Case is fictional
What would you estimate her creatinine clearance to be?

C. 40 mL/min
Patients With AF And Renal Impairment

- Every third patient with AF has chronic kidney disease (CKD)\(^1\)

- Prevalence of both AF and CKD increase with age\(^2\)

Frequency of CKD in AF patients\(^1\)

- Stage I and II: eGFR > 60 mL/min (67%)
- Stage III: eGFR 30-59 mL/min (30%)
- Stage IV: eGFR 15-29 mL/min (2%)
- Stage V: eGFR < 15 mL/min (1%)

Patients with AF and renal impairment

- Are at higher risk of bleeding and stroke than those with normal renal function\(^1\)
- Are more often undertreated with warfarin than those with normal renal function\(^2\)

---

Poor INR control = poor outcomes in AF patients

GARFIELD-AF Cohort 1

- Adequate control (n=1660)
- Poor control (n=2292)

(defined as <60% measurements within target range of INR 2–3; >55% of patients with INRs recorded)

NOACs (vs Warfarin) And Ischemic Stroke Or Bleeding: Patients With AF And CKD

Safety And Efficacy Of NOACs vs VKA In Patients With Renal Impairment

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild renal impairment</strong> (CrCl [eGFR] 50–79 ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major/NMCR bleeding</td>
<td>0.80 (0.71–0.90)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>0.70 (0.54–0.92)</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Moderate renal impairment</strong> (CrCl [eGFR] 30–49 ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major/NMCR bleeding</td>
<td>0.81 (0.54–1.21)</td>
<td>0.29</td>
</tr>
</tbody>
</table>
| Stroke/SE             | 0.72 (0.57–0.92)  | 0.008   

Favours NOAC     
Favours VKA

NOACs With Moderate Renal Impairment (CrCl 30-50 mL/min)

Rivaroxaban is the only NOAC that was prospectively studied according to dosing based solely on renal function

*1.5% of patients had CrCl 25-30 mL/min

Polling Question – Patient EF

What Oral Anticoagulant At Which Dose Would You Start?

D. Rivaroxaban 15 mg QD
NOAC Dosing Algorithms In AF

**Apixaban**

Patient has risk factor for stroke

Estimate CrCl

- <15 mL/min
  - Not recommended
  - No dosing recommendation can be made
- ≥15-24 mL/min
- ≥25 mL/min

Check age: Check weight, Check serum creatinine

- ≥80 years: <60 kg: ≥133 μmol/L
  - If ≥2 features: 2.5 mg BID
  - If ≤1 feature: 5 mg BID

---

**Dabigatran**

Patient has risk factor for stroke

Estimate CrCl

- <30 mL/min
  - Contraindicated
- 30-50 mL/min
  - Potential high bleeding risk?
    - Yes: Not recommended
    - No: 110 mg BID, 150 mg BID
- >50 mL/min
  - Age ≥75: 150 mg BID
  - Age 75-79: 150 mg (110mg if ≥1 risk factor for bleeding)
  - Age ≥80: 110 mg BID

---

**Rivaroxaban**

Patient has risk factor for stroke

Estimate CrCl

- <30 mL/min
  - Not recommended
- 30-49 mL/min
  - 15 mg OD
- >50 mL/min
  - 30 mg OD

---

Avoiding NSAIDs

- Apart from the issue of increased bleeding risk, NSAIDs should NOT be prescribed in individuals with hypertension, heart failure or CKD of all causes, including diabetes\(^1\)

- In these individuals, NSAIDS:
  - Elevate blood pressure
  - Make antihypertensive drugs less effective
  - Cause fluid retention
  - Worsen kidney function

CKD: chronic kidney disease; NSAIDs: nonsteroidal anti-inflammatory drugs.
Patient EF – 3 Months Later

- EF comes to the clinic with a UTI
  - Remains in AF, now at 80 BPM
  - BP 132/80 mmHg

<table>
<thead>
<tr>
<th>Labwork</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>116 μmol/L</td>
</tr>
<tr>
<td>CrCl</td>
<td>34 ml/min</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>118 g/L</td>
</tr>
<tr>
<td>Na⁺</td>
<td>137 mmol/L</td>
</tr>
<tr>
<td>K⁺</td>
<td>5.2 mmol/L</td>
</tr>
<tr>
<td>Urine</td>
<td>1+ proteinuria</td>
</tr>
</tbody>
</table>

Note: Case is fictional
### Acute Worsening Of Renal Function: Lower Rates of Stroke/Systemic Embolism With Apixaban

#### Outcomes By Renal Function Status

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>HR (95% CI)</th>
<th>HR</th>
<th>95% CI</th>
<th>p-int*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening Renal Function</td>
<td>0.78</td>
<td>0.54–1.11</td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Stable Renal Function</td>
<td>0.70</td>
<td>0.59–0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke/SE</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>Worsening Renal Function</td>
<td>0.83</td>
<td>0.52–1.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable Renal Function</td>
<td>0.75</td>
<td>0.59–0.94</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Worsening renal function=CrCl decrease of >20% from baseline

*Apixaban remains safe and effective in patients with worsening renal impairment*

*p-interaction for worsening renal function vs. stable renal function.

Acute Worsening Of Renal Function: 
Lower Rates of Stroke/Systemic Embolism With Rivaroxaban

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>By Renal Function Status</th>
<th>HR (95% CI)</th>
<th>HR</th>
<th>95% CI</th>
<th>p-int*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>Worsening Renal Function</td>
<td>1.06</td>
<td>0.61</td>
<td>0.80–1.39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stable Renal Function</td>
<td>0.98</td>
<td>0.61</td>
<td>0.89–1.08</td>
<td></td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>Worsening Renal Function</td>
<td>0.50</td>
<td>0.25</td>
<td>0.27–0.93</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>Stable Renal Function</td>
<td>0.97</td>
<td>0.25</td>
<td>0.76–1.24</td>
<td></td>
</tr>
</tbody>
</table>

Worsening renal function=CrCl decrease of >20% from baseline

Rivaroxaban remains safe and effective in patients with worsening renal impairment

*P-interaction for worsening renal function vs. stable renal function.

Total Drug Exposure With Declining Renal Function

- **Apixaban**¹
  (27% cleared renally)

- **Dabigatran**²
  (85% cleared renally)

- **Rivaroxaban**³
  (33% cleared renally)

- **Edoxaban**⁴
  (50% cleared renally)

### Creatinine Clearance (mL/min)

- ≥80
- 50-79
- 30-49
- <30

### AUC Ratio vs. Normal Renal Function

- Normal Renal Function: ≥80 mL/min; Mild Renal Impairment: 50-79 mL/min
- Moderate Renal Impairment: 30-49 mL/min; Severe Renal Impairment: <30 mL/min

---

Case – Patient IJ

- A 91-year-old man with a 10 year history of paroxysmal atrial fibrillation
  - Past medical history:
    - Hypertension, past smoker
    - Prior TIA, prior GI bleed (due to H. Pylori and appropriately treated)
  - Physical examination:
    - HR 98 bpm, irreg irreg; BP 136/90 mmHg
    - Chest and CVS examinations otherwise normal
  - Medication:
    - Bisoprolol 10 mg once daily, amlodipine 10 mg once daily, apixaban 5.0 mg once daily
  - Investigations:
    - CrCl = 62 ml/min, otherwise unremarkable

Perhaps a physician fear of bleeding given HAS-BLED = 4 ?

Note: Case is fictional
Bleeding Risk Avoidance

- Address reversible risk factors:
  - Falling → provide mobility aid
  - Hypertension → treat blood pressure to target
  - Alcohol → encourage abstinence
  - Labile INR → use NOACs
  - Drugs → replace NSAIDs with other analgesics, avoid ASA unless clearly indicated for secondary prevention
  - GI bleeding → use proton pump inhibitors (PPI)

*Bleeding risk should not usually be a reason to preclude optimal treatment*
A Matter Of Perception
Dosing Disconnect With Physicians: Likely Related to Fear of Bleeding

Patients place more weight on the risk of stroke

Concern about bleeding (unless patient risk is extreme) should not lead to the underdosing, let alone withholding, of anticoagulant therapy

Real World vs Phase III Trial And Real World NOAC Dosing: Underdosing May Negatively Impact Expected Outcomes

Patients Receiving Adjusted Dose Of Rivaroxaban Or Apixaban

ROCKET AF\textsuperscript{1}  
- Low-dose rivaroxaban (15 mg od): 20.7%  
- High-dose rivaroxaban (20 mg od): 79.3%

IMS LifeLink\textsuperscript{2}  
- Low-dose rivaroxaban (15 mg od): 21.7%  
- High-dose rivaroxaban (20 mg od): 78.3%

ARISTOTLE\textsuperscript{3}  
- Low-dose apixaban (2.5 mg bid): 4.7%  
- High-dose apixaban (5 mg bid): 95.3%

IMS LifeLink\textsuperscript{2}  
- Low-dose apixaban (2.5 mg bid): 20.8%  
- High-dose apixaban (5 mg bid): 79.2%

REASSESS\textsuperscript{4*}  
- Low-dose apixaban (2.5 mg bid): 35.2%  
- High-dose apixaban (5 mg bid): 64.8%

Real-world usage of **low-dose** apixaban is substantially and disproportionately higher than in the phase III populations

\textsuperscript{1} Pre-specified re-analysis (patients with at least 360 days of follow-up)  
\textsuperscript{2} IMS LifeLink = US administrative data  
\textsuperscript{3} REASSESS = German registry data  
\textsuperscript{4} Not intended as cross-study comparison

## Reasons for Dose Adjustment Varied Between NOAC Trials

<table>
<thead>
<tr>
<th></th>
<th>ARISTOTLE(^1)</th>
<th>RE-LY(^2)</th>
<th>ENGAGE AF(^3)</th>
<th>ROCKET AF(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose (adjusted dose)</strong></td>
<td>5 mg bid (2.5 mg bid)</td>
<td>150 mg bid (110 mg bid)</td>
<td>60 mg bid (30 mg bid) or 30 mg bid (15 mg bid)</td>
<td>20 mg od (15 mg od)</td>
</tr>
</tbody>
</table>
| **Criteria for dose adjustment** | Dose adjustment at randomization if ≥2 of the following:  
- Age ≥80 years  
- Weight ≤60 kg  
- Creatinine ≥133 μmol/l | None (randomized to one of two doses) | Dose adjustment at randomization or throughout for ≥1 of the following:  
- CrCl 30–49 ml/min  
- Weight ≤60 kg  
- Strong P-gp inhibitors | CrCl 30–49 ml/min |
| **Patients receiving adjusted dose, %** | 4.7 | 49.7 | 25.4 | 20.7 |

Inappropriate dosing can increase a patient’s risk of stroke

Patients Initiating NOACs Without A Renal Indication For Dose Adjustment
US Insurance Claims Database
(1 Oct 2010–30 Sep 2015)

<table>
<thead>
<tr>
<th></th>
<th>Event Rate per 100 person-years</th>
<th>Hazard Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced Dose</td>
<td>Standard Dose</td>
<td></td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>N=550</td>
<td>N=550</td>
<td></td>
</tr>
<tr>
<td>S/SE</td>
<td>2.57</td>
<td>0.54</td>
<td>4.87 (1.30-18.26)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>6.01</td>
<td>4.64</td>
<td>1.29 (0.48-3.42)</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>N=412</td>
<td>N=412</td>
<td></td>
</tr>
<tr>
<td>S/SE</td>
<td>1.64</td>
<td>1.75</td>
<td>0.92 (0.30-2.87)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>4.99</td>
<td>5.54</td>
<td>0.91 (0.45-1.85)</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>N=815</td>
<td>N=815</td>
<td></td>
</tr>
<tr>
<td>S/SE</td>
<td>1.23</td>
<td>1.65</td>
<td>0.71 (0.24-2.09)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>5.42</td>
<td>4.90</td>
<td>1.09 (0.63-1.87)</td>
</tr>
</tbody>
</table>

*Propensity-score matched based on 50 socio-demographic characteristics, co-morbidities and baseline medication use

Yao et al. JACC 2017:2779–90.
Prescribing Patterns of NOACs Globally by Dose: Results from the 4th Quarter of 2015

<table>
<thead>
<tr>
<th>Country</th>
<th>Apixaban(^1) Q4 2015</th>
<th>Dabigatran(^1) Q4 2015</th>
<th>Rivaroxaban(^1) Q4 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5 mg</td>
<td>5 mg</td>
<td>75 mg</td>
</tr>
<tr>
<td>UNITED STATES</td>
<td>25%</td>
<td>75%</td>
<td>16%</td>
</tr>
<tr>
<td>GERMANY</td>
<td>43%</td>
<td>57%</td>
<td>1%</td>
</tr>
<tr>
<td>CANADA</td>
<td>37%</td>
<td>63%</td>
<td>1%</td>
</tr>
<tr>
<td>AUSTRALIA</td>
<td>40%</td>
<td>60%</td>
<td>0%</td>
</tr>
<tr>
<td>UNITED KINGDOM</td>
<td>37%</td>
<td>62%</td>
<td>2%</td>
</tr>
<tr>
<td>SPAIN</td>
<td>39%</td>
<td>61%</td>
<td>2%</td>
</tr>
<tr>
<td>BELGIUM</td>
<td>31%</td>
<td>69%</td>
<td>0%</td>
</tr>
<tr>
<td>ITALY</td>
<td>37%</td>
<td>63%</td>
<td>0%</td>
</tr>
<tr>
<td>AVERAGE LOW DOSE</td>
<td>36%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Phase III studies

<table>
<thead>
<tr>
<th></th>
<th>ARISTOTLE(^2)</th>
<th>RE-LY(^3)</th>
<th>ROCKET AF(^4,5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.7%</td>
<td>95.3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

In practice, prescriptions for apixaban at the lower 2.5 mg dose are disproportionately high. Similar but less-marked patterns are seen with dabigatran and rivaroxaban.

NOACs and major bleeding: the clinical trials

### Major bleeding

<table>
<thead>
<tr>
<th>Trial</th>
<th>NOAC (events)</th>
<th>Warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY^5^</td>
<td>375/6076</td>
<td>397/6022</td>
<td>0.94 (0.82–1.07)</td>
<td>0.34</td>
</tr>
<tr>
<td>ROCKET AF^6^†</td>
<td>395/7111</td>
<td>386/7125</td>
<td>1.03 (0.90–1.18)</td>
<td>0.72</td>
</tr>
<tr>
<td>ARISTOTLE^7^†</td>
<td>327/9088</td>
<td>462/9052</td>
<td>0.71 (0.61–0.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48^8^§</td>
<td>444/7012</td>
<td>557/7012</td>
<td>0.80 (0.71–0.90)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>1541/29287</td>
<td>1802/29211</td>
<td>0.86 (0.73–1.00)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

### Intracranial and gastrointestinal bleeding

<table>
<thead>
<tr>
<th>Category</th>
<th>Pooled NOAC (events)</th>
<th>Pooled warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>204/29287</td>
<td>425/29211</td>
<td>0.48 (0.39–0.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>751/29287</td>
<td>591/29211</td>
<td>1.25 (1.01–1.55)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

CT Ruff, Lancet 2014
Warfarin
Poor INR control = poor outcomes in AF patients

GARFIELD-AF Cohort 1

- Adequate control (n=1660)
- Poor control (n=2292)

Events per 100 patient years

- Stroke/TIA: 1.2
- Major bleed: 0.5
- Death: 1.0

(defined as <60% measurements within target range of INR 2–3; >55% of patients with INRs recorded)

Why time in therapeutic range (TTR) matters

---

# VKA Major Bleeding in Daily Care

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Rate of major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beyth; Am J Med. 1998</td>
<td>820 VKA starter</td>
<td>6.5%/a</td>
</tr>
<tr>
<td>Gitter; Mayo Clin Proc. 1995</td>
<td>261 Warfarin pts.</td>
<td>5.3% in first year</td>
</tr>
<tr>
<td>Steffensen; J Intern Med 1997</td>
<td>682 VKA starter</td>
<td>6.0%/100 pt.-years</td>
</tr>
<tr>
<td>Willey; Clinical Therapeutics 2004</td>
<td>2090 pts. with new VTE</td>
<td>Hospitalization: 12.6/100 pt.-years</td>
</tr>
<tr>
<td>Gomes; CMAJ 2012</td>
<td>125,195 Warfarin starters</td>
<td>3.8%/pt.-years</td>
</tr>
<tr>
<td>Linkins; Ann Intern Med. 2003</td>
<td>Meta-analysis of 33 VTE studies; 10,757 pts.</td>
<td>7.2%/100 pt.-years</td>
</tr>
<tr>
<td>Halbritter; JTH 2013</td>
<td>Hospitalization for VKA bleeding</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

**Rate:** ~6–8% per year

**Trials:**
- ROCKET 3.4 %pt-years
- ARISTOTLE 3.1%/year
- RE-LY 3.36%/year

Major Bleeding Rates with Rivaroxaban in Real World Studies were Consistent with Findings from ROCKET AF

**Major bleeding definitions according to ISTH; **modified ISTH definition (additionally included surgical revision from bleeding)

Results are not intended for direct comparison

US DoD PMSS = US Department of Defense Post-Marketing Surveillance Study

*Major bleeding was defined by the Cunningham algorithm*

**US DoD PMSS = US Department of Defense Post-Marketing Surveillance Study**

**Results are not intended for direct comparison**
Effect of PCC on rivaroxaban

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate
A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects
Elise S. Eerenberg, MD; Pietro W. Kampshoff, MD; Meretein K. Sigkess, BSc;
Joon C. Meijers, PhD; Harry R. Baller, MD; Marcel Levi, MD

Vitamin K antagonists have been the only oral anticoagulants for decades despite their unpredictable pharmacology and their slow onset and offset of action. Vitamin K antagonists require frequent monitoring because of a substantial risk of under- or overtreatment. Several new oral anticoagulants with more stable pharmacokinetic and pharmacodynamic profiles have been licensed for clinical practice or are in the final stage of clinical development. At this moment, dabigatran (a direct thrombin inhibitor) and rivaroxaban (a direct factor Xa inhibitor) are the most extensively evaluated novel anticoagulant agents. Both anticoagulants have little interaction with food or drugs and can therefore be prescribed in a fixed dose without the requirement of frequent monitoring. They have been shown to be effective and safe in large trials in the prevention and treatment of venous thromboembolism (VTE) and prevention of stroke in atrial fibrillation. This has led to the registration of both drugs in Europe and Canada for the prevention of VTE in elective orthopedic surgery. Dabigatran has also been licensed recently in Canada and the United States for stroke prevention in atrial fibrillation; registration in Europe will probably follow soon. For rivaroxaban, a submission for stroke prevention in atrial fibrillation treatment was filed in the United States and Europe.

Clinical Trial Registration—URL: http://www.trialregister.nl. Unique identifier: NTR2272. (Circulation. 2011;124:1573-1579.)

Key Words: anticoagulants • coagulation • hemorrhage • thrombosis • trials
Protocol and main results

Rivaroxaban Prothrombin Time

- The PT was significantly prolonged by rivaroxaban (15.8±1.3 versus 12.3±0.7 seconds at baseline; \( P<0.001 \))
- Immediately after the infusion of PCC, the PT completely normalized (12.8±1.0 seconds; \( P<0.001 \)), which was sustained for 24 hours

Methods and Results—In a randomized, double-blind, placebo-controlled study, 12 healthy male volunteers received rivaroxaban 20 mg twice daily (n=6) or dabigatran 150 mg twice daily (n=6) for 2½ days, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline. After a washout period, this procedure was repeated with coagulation tests.
Reversal agents
Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S.,
Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D.,
Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D.,
Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D.,
Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D.,
Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and
Jeffrey I. Weitz, M.D.
Idarucizumab characteristics (I)

- Competes with thrombin for binding of dabigatran
- 350-fold higher affinity
- No coagulation activity

Data collected from in vitro study; Schiele F et al. Blood 2013;121:3554–62
Andexanet alfa (PRT06445)

- Reversal agent to the xabans
- **Recombinant FXa** modified without catalytic activity
- High affinity for direct FXa inhibitors (Xabans) and for heparin-antithrombin complexes and fondaparinux

*Siegal, N Engl J Med, 2015*
Andexanet alfa (PRT06445)

Specific anti-Xa activity

**A** Apixaban Study, Andexanet Bolus

- **Apixaban**
- **Rivaroxaban**

**B** Rivaroxaban Study, Andexanet Bolus

- **Placebo (N=9)**
- **Andexanet (N=24)**

- **Placebo (N=14)**
- **Andexanet (N=27)**

**C** Apixaban Study, Andexanet Bolus plus Infusion

- **Placebo (N=8)**
- **Andexanet (N=23)**

**D** Rivaroxaban Study, Andexanet Bolus plus Infusion

- **Placebo (N=13)**
- **Andexanet (N=26)**

_Siegal, N Engl J Med, 2015_
Ciraparantag (PER977)

Aripazine

A cationic molecule capable of binding non-covalently to FXa and thrombin inhibitors, fondaparinux, and LMWH

Development stage:
- In vitro: inhibition of apixaban, rivaroxaban and enoxaparin
- Reduction of bleeding > 90 % in rats exposed to overdosage in dabigatran, rivaroxaban, apixaban or edoxaban
- Healthy volunteers: standardisation of coagulation times (edoxaban) stable beyond 24 hours

General measures to control bleeding

• Hold antithrombotic drug ("tincture of time")
• Identify / control source of bleeding
  – Local / surgical hemostasis
• Volume replacement / blood transfusion
NOACs and bleeding

Key questions

• How much drug is on board?
• How long will the drug be on board?
• How can I reduce drug levels?
• How can I reverse drug effects?
NOACs and bleeding
Evaluation of effect of the anticoagulant

• Determine timing of last dose of drug
• Measure creatinine (NOACs)
• Measure anticoagulant activity