Anticoagulation in frail and complex patients

Dr Will Lester

Summary

- The definition of frailty is broad and can be used to describe a wide range of conditions in older people.
- Frailty is associated with an increased risk of adverse outcomes, including falls, hospitalization, and death.
- Chronic kidney disease (CKD) is a condition that affects the kidneys and can lead to complications such as anemia, hypertension, and cardiovascular disease.
- Frailty and CKD can increase the risk of bleeding and thrombosis.

Anticoagulation in the frail

- Restarting anticoagulation after a bleed
- Oral anticoagulants combined with anti-platelet drugs

Oral anticoagulants and anti-platelet drugs

- Oral anticoagulants are associated with a higher risk of bleeding

Chronic kidney disease and falls

- CKD can lead to anemia and an increased risk of falls.
Anticoagulation in frail and complex patients

Dr Will Lester

Summary

- Anticoagulation in the frail
  - Restarting anticoagulation after a bleed
  - Oral anticoagulants combined with anti-platelet drugs

Chronic kidney disease and falls

Oral anticoagulants and anti-platelet drugs

Age combinations are associated with an increased risk of bleeding.
- Anticoagulation in the frail
- Restarting anticoagulation after a bleed
- Oral anticoagulants combined with anti-platelet drugs
## Declarations

<table>
<thead>
<tr>
<th>Category</th>
<th>Company Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speaker honoraria</td>
<td>Boehringer Ingelheim, Bayer, Bristol Myers</td>
</tr>
<tr>
<td></td>
<td>Squibb, LEO Pharma, Pfizer, Roche</td>
</tr>
<tr>
<td>Advisory board</td>
<td>Boehringer Ingelheim, Bayer, Bristol Myers</td>
</tr>
<tr>
<td></td>
<td>Squibb, Daiichi Sankyo, Pfizer</td>
</tr>
<tr>
<td>Support to attend scientific meeting:</td>
<td>Boehringer Ingelheim</td>
</tr>
</tbody>
</table>
Which anticoagulant is more appealing?

Drug A:
Slightly more effective than warfarin with the same bleeding risk

Drug B:
As effective as warfarin with a lower risk of bleeding
Frailty

In next 30 years in the UK (ONS):

- Over triple the number aged >90 years
- Over quadruple aged >95 years
- Eightfold increase aged >100 years
Managing complex patients: no easy answer

- Trial sub-analysis
- Post marketing studies
- ‘Real world’ data eg. registries/databases
- Personal experience
- Pragmatism
Case 1

• 86 year old female is admitted with CVA
  – Hypertension
  – eGFR 41ml/min
  – 49kg
  – Lives alone
  – Early symptoms of dementia?
  – Known AF and is on aspirin on admission
• Makes a good recovery and is transferred to the local rehab hospital
• What are you going to do about anticoagulation?

Issues to explore

Patient/carer opinion
Adherence with medicines/dosette box
Responsibility to wider health economy
Case 1

• 86 year old female is admitted with CVA
  – Hypertension
  – eGFR 41ml/min
  – 49kg
  – Lives alone
  – Early symptoms of dementia?
  – Known AF and is on aspirin on admission

• Makes a good recovery and is transferred to the local rehab hospital

• What are you going to do about anticoagulation?
Issues to explore

Patient/carer opinion
Adherence with medicines/dosette box
Responsibility to wider health economy
GARFIELD registry

**WHY IS ASPIRIN USED DESPITE HIGH STROKE RISK?**

Evidence

Oral anticoagulation or nothing

BAFTA results: primary end point

Risk of primary end point:
Warfarin vs aspirin
- 1.8% p.a. vs 3.8% p.a.
- RR 0.48 (0.29-0.80)
- p = 0.0027
- NHL: 50 for 1 year

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>21</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Subdural</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Embolism</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>48</td>
</tr>
</tbody>
</table>

BAFTA Secondary outcomes:
haemorrhage – risk per annum

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major extra-cranial</td>
<td>1.4%</td>
<td>1.6%</td>
<td>0.87 (0.43-1.73)</td>
</tr>
<tr>
<td>Other hospital admission</td>
<td>1.8%</td>
<td>1.5%</td>
<td>1.22 (0.64-2.36)</td>
</tr>
<tr>
<td>All major (including stroke and subdural)</td>
<td>1.9%</td>
<td>2.0%</td>
<td>0.96 (0.53-1.75)</td>
</tr>
</tbody>
</table>

AVEROES:
TIA: the all stroke trial
Aspirin vs warfarin in AF

[Graphs and charts]

- Graph A: Distribution of stroke and hemorrhage
- Graph B: Risk of major hemorrhage
**BAFTA results: primary end point**

Risk of primary end point:
- *Warfarin v aspirin*
  - 1.8% p.a v 3.8% p.a
  - RR 0.48 (0.28-0.80)
  - p = 0.0027
- NNT: 50 for 1 year

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td>-ischaemic</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>-haem</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>Subdural</strong></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Embolism</strong></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>24</td>
<td>48</td>
</tr>
</tbody>
</table>
# BAFTA Secondary outcomes: haemorrhage – risk per annum

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major extra-cranial</td>
<td>1.4%</td>
<td>1.6%</td>
<td>0.87 (0.43-1.73)</td>
</tr>
<tr>
<td>Other hospital admission</td>
<td>1.8%</td>
<td>1.5%</td>
<td>1.22 (0.64-2.36)</td>
</tr>
<tr>
<td>All major (including stroke and sub-dural)</td>
<td>1.9%</td>
<td>2.0%</td>
<td>0.96 (0.53-1.75)</td>
</tr>
</tbody>
</table>
AVERROES:
N Engl J Med 2011; 364:806

Aspirin vs Apixaban in SPAF
Chronic kidney disease and falls

Falls

1/3rd patients >65 years fall every year; 10% result in serious injury

HARDER
1. Predictive modeling from literature review: patient with AF and 5% stroke risk would need to fall 295 times a year in order to benefit from anticoagulation
2. Reduction in death/hospitalisation in patients on warfarin with falls greater than the increased risk of intracranial bleeding in retrospective study if CHADS2 2.2
3. No significant increase in bleeds in falls patients in prospective study

DOAC dose adjustments for renal disease
- Dabigatran: 110mg bid for GFR 30-50ml/min
- Rivaroxaban: 15mg od for GFR 15-50ml/min
- Apixaban: 2.5mg bid for GFR 15-30ml/min or oral, 0.75mg daily
- Edoxaban: 30mg od for GFR 15-50ml/min
Falls

1/3rd patients >65 years fall every year; 10% result in serious injury

HOWEVER
1. Predictive modeling from literature review; patient with AF and 5% stroke risk would need to fall 295 times a year to lose benefit from anticoagulation
2. Reduction in death/hospitalisation in patients on warfarin with falls greater than the increased risk of intracranial bleeding in retrospective study if CHADS2 ≥2
3. No significant increase in bleeds in falls patients in prospective study

1. Man-Son Hing et al Arch Intern Med 1999; 159: 677-85
Chronic kidney disease
Chronic kidney disease is common among AF patients

Leiden Anticoagulation Clinic (n=5,039; 1997–2005)

- eGFR, mL/min/1.73 m² (MDRD formula)
- % of patients
  - >60: 65.8%
  - 30–60: 30.9%
  - 15–30: 2.5%
  - 0–15: 0.8%

AURICULA Registry, Malmö (n=2,603; 2007–2008)

- eGFR, mL/min/1.73 m² (MDRD formula)
- % of patients
  - <60: 40.4%
  - <45: 16.3%
  - <30: 4.3%

Chronic kidney disease is common among AF patients

Leiden Anticoagulation Clinic (n=5,039; 1997–2005)

- 65.8% >60
- 30.9% 30–60
- 2.5% 15–30
- 0.8% 0–15

AURICULA Registry, Malmö (n=2,603; 2007–2008)

- 40.4% <60
- 16.3% <45
- 4.3% <30

Outcome: Major Bleeding

1 Year event rate

Baseline Cockcroft-Gault eGFR mL/min

P-value for Interaction = 0.005

- Warfarin
- 95% CI
- Apixiban
- 95% CI
Outcome: Stroke or Systemic Embolism

![Graph showing the outcome of stroke or systemic embolism based on baseline Cockcroft-Gault eGFR mL/min. The graph compares Warfarin with Apixaban, showing the 95% confidence interval (CI) for each. The P-value for interaction is 0.57.]
DOAC dose adjustments for renal disease

- Dabigatran: 110mg bd for GFR 30-50ml/min
- Rivaroxaban: 15mg od for GFR 15-50ml/min
- Apixaban: 2.5mg bd for GFR 15-30ml/min or Creat >133umol/L and either age ≥80 or weight ≤60kg
- Edoxaban 30mg od for GFR 15-50ml/min
Oral anticoagulants and anti-platelet drugs

ALL combinations are associated with a higher risk of bleeding

HAS-BLED

Management of AF patients with Acute Coronary Syndrome or Percutaneous coronary Intervention
European Heart Journal
doi:10.1093/eurheartj/ehu298
Arch Intern Med 2010;170:1433

- Warfarin monotherapy: 1 [Reference]
- Aspirin monotherapy: 0.93 (0.88-0.98)
- Clopidogrel monotherapy: 1.06 (0.87-1.29)
- Aspirin + clopidogrel: 1.66 (1.34-2.04)
- Warfarin + aspirin: 1.83 (1.72-1.96)
- Warfarin + clopidogrel: 3.08 (2.32-3.91)
- Triple therapy: 3.70 (2.89-4.76)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H</strong> Hypertension: (uncontrolled, &gt;160 mmHg systolic)</td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong> Abnormal renal function: Dialysis, transplant, Cr &gt;2.6 mg/dL or &gt;200 µmol/L</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal liver function: Cirrhosis or Bilirubin &gt;2x Normal or AST/ALT/AP &gt;3x Normal</td>
<td>1</td>
</tr>
<tr>
<td><strong>S</strong> Stroke: Prior history of stroke</td>
<td>1</td>
</tr>
<tr>
<td><strong>B</strong> Bleeding: Prior Major Bleeding or Predisposition to Bleeding</td>
<td>1</td>
</tr>
<tr>
<td><strong>L</strong> Labile INR: (Unstable/high INRs), Time in Therapeutic Range &lt;60%</td>
<td>1</td>
</tr>
<tr>
<td>Elderly: Age &gt; 65 years</td>
<td>1</td>
</tr>
<tr>
<td><strong>E</strong> Medication Usage Predisposing to Bleeding: (Antiplatelet agents, NSAIDs)</td>
<td>1</td>
</tr>
<tr>
<td><strong>D</strong> Prior Alcohol or Drug Usage History</td>
<td>1</td>
</tr>
</tbody>
</table>
Management of AF patients with Acute Coronary Syndrome or Percutaneous coronary Intervention
European Heart Journal
doi:10.1093/eurheartj/ehu298
What to do after bleeding?

Gastrointestinal bleeding
- If on VKA, was the INR high?
- Is it a treatable lesion eg. ulcer?
- NSAIDs or antplatelet use?
- Risk of thrombosis off anticoagulation vs risk bleeding if continued

Intra-cranial bleeding
Up to 45% of patients presenting with chronic subdural haematoma are on anticoagulants

Considerations:
- ICH in deep location - 2% annual recurrence
- Lobar ICH - 4% annual recurrence

Alternatives to anticoagulation
Gastrointestinal bleeding

- If on VKA, was the INR high?
- Is it a treatable lesion eg. ulcer?
- NSAIDs or antiplatelet use?
- Risk of thrombosis off anticoagulation vs risk bleeding if continued
Meta-Analysis of Efficacy and safety of DOAC’s
Am J Cardiol 2012;110:453-460

A: Major bleeding
- RE-LY
- ROCKET AF
- ARISTOTLE
Subtotal (I-squared = 87.2%, p = 0.000)

B: Intracranial bleed
- RE-LY
- ROCKET AF
- ARISTOTLE
Subtotal (I-squared = 54.9%, p = 0.109)

C: GI bleeding
- RE-LY
- ROCKET AF
- ARISTOTLE
Subtotal (I-squared = 82.5%, p = 0.003)
Intra-cranial bleeding

Up to 43% of patients presenting with chronic subdural haematoma are on anticoagulants

Considerations:
ICH in deep location - 2% annual recurrence
Lobar ICH - 4% annual recurrence
Stroke. 2010;41:2860-2866
Outcome of bleeding on DOAC vs VKA
All cause death after major bleeding in ARISTOTLE trial
Held et al 2014 European Heart Journal
http://dx.doi.org/ezproxye.bham.ac.uk/10.1093/eurheartj/ehu463
Alternatives to anticoagulation
PROTECT AF
Circulation. 2013;127:720-9

A Primary efficacy end point

HR (95% CI), 0.61 (0.38-0.97)
P = .04

B Primary safety end point

HR (95% CI), 1.21 (0.78-1.94)
P = .41

No. of patients
Device
Warfarin

463 398 382 370 360 345 337 327 285 196
244 230 218 210 200 188 173 159 147 121 87
463 376 364 357 353 341 332 320 310 277 190
244 228 214 207 195 183 169 153 139 117 86
Summary

• The application of trial data to frail patients with multiple co-morbidities is a conundrum
• Assessing benefits and risks of anticoagulation in patients at high risk of bleeding is complex as the risks of thrombosis is also increased eg. chronic kidney disease
• Co-prescription of oral anticoagulants with anti-platelet agents should be avoided unless essential
• Some forms of oral anticoagulation may be more appropriate in certain circumstances eg. renal failure, GI bleeding, intracranial bleeding
• Alternatives to anticoagulation may sometimes be available eg. atrial appendage occlusion devices